

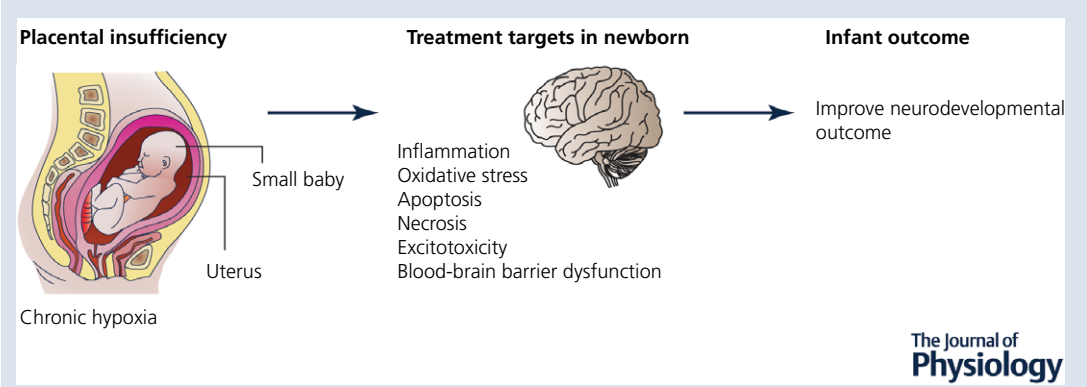
TOPICAL REVIEW

Therapeutic potential to reduce brain injury in growth restricted newborns

Julie A. Wixey , Kirat K. Chand , Lily Pham , Paul B. Colditz  and S. Tracey Bjorkman 

UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, Queensland, 4029, Australia

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Placental insufficiency

Small baby
Uterus
Chronic hypoxia

Treatment targets in newborn

Inflammation
Oxidative stress
Apoptosis
Necrosis
Excitotoxicity
Blood-brain barrier dysfunction

Infant outcome

Improve neurodevelopmental outcome

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Abstract Brain injury in intrauterine growth restricted (IUGR) infants is a major contributing factor to morbidity and mortality worldwide. Adverse outcomes range from mild learning difficulties, to attention difficulties, neurobehavioral issues, cerebral palsy, epilepsy, and other cognitive and psychiatric disorders. While the use of medication to ameliorate neurological deficits in IUGR neonates has been identified as warranting urgent research for several years, few trials have been reported. This review summarises clinical trials focusing on brain protection in the IUGR newborn as well as therapeutic interventions trialled in animal models of IUGR. Therapeutically targeting mechanisms of brain injury in the IUGR neonate is fundamental to improving long-term neurodevelopmental outcomes. Inflammation is a key mechanism in neonatal brain injury; and therefore an appealing target. Ibuprofen, an anti-inflammatory drug currently used in the preterm neonate, may be a potential therapeutic candidate to treat brain injury in the IUGR neonate. To better understand the potential of ibuprofen and other therapeutic agents to be neuroprotective in the IUGR neonate, long-term follow-up information of neurodevelopmental outcomes must be studied. Where agents such as ibuprofen are shown to be effective, have a good safety profile and are relatively inexpensive, they can be widely adopted and lead to improved outcomes.

Julie Wixey is a Postdoctoral Researcher at the Perinatal Research Centre, The University of Queensland Centre for Clinical Research under the supervision of Professor Paul Colditz. She received her PhD from The University of Queensland in 2013. Her research focuses on the role of inflammation in perinatal brain injury; such as intrauterine growth restriction, hypoxia–ischaemia and preterm birth. Her goal is to develop neuroprotective therapies to reduce brain injury in these babies. **Kirat Chand** is an Early Career Researcher who received his PhD from The University of Queensland in 2015. He joined the Perinatal Research Centre as a Postdoctoral Researcher in 2016 under the supervision of Dr Tracey Björkman. His research focuses on perinatal brain injury, with a particular interest in the role of neuroinflammation and its contribution in progression of injury in the newborn brain.



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Corresponding author J. A. Wixey: UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, Queensland 4029, Australia. Email: j.wixey@uq.edu.au

Abstract figure legend Several mechanisms are considered to mediate brain injury in the growth restricted newborn including inflammation, oxidative stress, apoptosis and necrosis, excitotoxicity and blood-brain barrier dysfunction. Therapeutically targeting these mechanisms of injury could improve neurodevelopmental outcomes in the growth restricted newborn.

Introduction

Intrauterine growth restriction (IUGR) is a condition where a fetus fails to achieve appropriate growth due to a suboptimal environment and is a major cause of perinatal mortality and morbidity (Regev *et al.* 2003; Laws *et al.* 2006). IUGR and small for gestational age (SGA) have been used interchangeably in medical literature; however, small differences exist between the two conditions. Small for gestational age (SGA) only considers weight at birth and is defined as a birth weight below the 10th percentile. While birth weight is taken into account, IUGR is further defined by physiological determinants and neonatal features of malnutrition and *in utero* growth retardation (Sharma *et al.* 2016). The most common cause of IUGR is placental insufficiency with restricted blood flow to the placenta resulting in an inadequate supply of nutrients and oxygen to support normal growth of the fetus (Sharma *et al.* 2016). Growth of the fetus in a chronic hypoxic environment affects the development of numerous organ systems including the fetal brain which is particularly vulnerable (Miller *et al.* 2016). Factors associated with abnormal brain development in the IUGR fetus/newborn include preterm birth, timing of placental insufficiency and whether the brain growth measured as head circumference has been compromised, onset and subsequent severity of fetal compromise, fetal cerebrovascular response and the redistribution of blood flow, and other co-existing pregnancy complications.

Both structural and functional brain deficits are observed in IUGR neonates (reviewed in Miller *et al.* 2016). Clinical imaging studies of IUGR infants demonstrate alterations in grey matter and white matter volume and structure (Tolsa *et al.* 2004; Esteban *et al.* 2010; Padilla *et al.* 2015). Furthermore, these structural changes are still evident at 1 year of age and are associated with significant developmental disabilities (Tolsa *et al.* 2004; Esteban *et al.* 2010). Adverse neurological outcomes associated with IUGR range from mild learning difficulties, to attention difficulties, neurobehavioral issues, cerebral palsy (CP), altered sensory organ function, epilepsy, and other cognitive and psychiatric disorders (Jarvis *et al.* 2003; Ozanne *et al.* 2004; Geva *et al.* 2006; Freire *et al.* 2015). Key developmental processes are likely to underpin brain damage in IUGR infants offering

the potential for targeted treatments to improve neurodevelopmental outcomes.

Brain injury in IUGR. Mechanisms of brain injury in the IUGR neonate are complex and not well understood. The IUGR fetal brain is occasionally referred to as hypoxic–ischaemic (HI) (Rees *et al.* 2011) but the brain may not be globally ischaemic as a differential distribution of cerebral blood flow occurs to regions of the brain over time (Hernandez-Andrade *et al.* 2008). However the IUGR fetus is relatively hypoxic due to placental insufficiency, which may compromise cerebral blood perfusion and delivery of oxygen to the brain (Rees *et al.* 2011). These fluctuations initiate a cascade of biochemical and cellular events that result in cellular injury. Several mechanisms mediate cellular injury in the IUGR brain, including excitotoxicity, oxidative stress, blood–brain barrier (BBB) disruption, necrotic and apoptotic degeneration and neuroinflammation and its further pathways to injury (Rees *et al.* 2011; Miller *et al.* 2016). Animal studies demonstrate these events occur *in utero* (Rees *et al.* 2011; Castillo-Melendez *et al.* 2015; Miller *et al.* 2016; Alves de Alencar Rocha *et al.* 2017) and evolve throughout gestation, with some recent studies demonstrating the injurious mechanisms continuing into the newborn/adolescent period (Olivier *et al.* 2005, 2007; Black *et al.* 2015; Pham *et al.* 2015). Altered growth processes in the brain may also have occurred *in utero* over some days/weeks. Growth is an energy consuming process and when brain oxygenation becomes compromised growth processes within the brain could be altered including neurogenesis, synaptogenesis and myelination. Although these alterations may occur *in utero*, they may be amenable to postnatal therapeutic interventions. Therefore it is critical to ascertain which mechanisms continue following birth, and for how long.

Inflammation in the IUGR brain. Neuroinflammation is emerging as one of the key mechanisms that mediates abnormal brain development in IUGR neonates (Wixey *et al.* 2017). Neuroinflammation encompasses a number of processes and is characterised by increased numbers of activated microglia, elevated levels of proinflammatory cytokines (such as interleukin-1 β and tumour necrosis factor- α), decreased production of anti-inflammatory cytokines, and astrogliosis (Cai *et al.* 2006; Kremlev *et al.*

2007; Carty *et al.* 2008; Leonardo *et al.* 2008; Huang *et al.* 2009; Wixey *et al.* 2009, 2011). Recent animal studies demonstrate increased activated microglia and astrogliosis in the IUGR brain, indicative of an inflammatory response (Olivier *et al.* 2005, 2007; Guo *et al.* 2010; Tolcos *et al.* 2011; Black *et al.* 2015; Pham *et al.* 2015; Wixey *et al.* 2017). There are also indications from these studies that neuroinflammation may be associated with neuronal and white matter injury in the IUGR brain (Olivier *et al.* 2007; Guo *et al.* 2010; Pham *et al.* 2015). Severe inflammation (microglial activation and astrogliosis) in the brain is evident and closely aligns with a delay in myelination and white matter lesions in rat models of IUGR (Olivier *et al.* 2007; Pham *et al.* 2015). In guinea-pig models of IUGR, increases in interleukin- 1β (IL- 1β) and tumour necrosis factor- α (TNF- α) in the fetal brain correlate with worsening brain injury (Guo *et al.* 2010).

While there is evidence of a direct inflammatory response in the brain of IUGR neonates, the role of systemic inflammation in mediating brain injury is also gaining attention. In a recent human study, systemic inflammation, as demonstrated by elevated concentrations of proinflammatory cytokines in blood, is associated with abnormal neurodevelopment and poorer neurological outcomes in IUGR neonates (McElrath *et al.* 2010). Under normal conditions the brain is protected from harmful systemic toxins by the BBB. Alterations in BBB composition have been reported in IUGR neonates (Castillo-Melendez *et al.* 2015, 2017). Decreased BBB integrity may result in an increased infiltration of systemic inflammatory mediators into the brain, further exacerbating the neuroinflammatory response. Likewise, BBB breakdown may facilitate the passage of brain-derived inflammatory cells into the blood resulting in heightened systemic responses.

It is unclear whether neuroinflammation is a direct cause of brain injury in the IUGR fetus/newborn or is a secondary response to cellular injury. Whilst much of the focus is on the detrimental effects of proinflammatory cytokines, targeting the activation of anti-inflammatory cytokines may play a role in protecting the brain. Examination of both pro- and anti-inflammatory cytokine responses in the IUGR newborn is important, as both pathways could be exploited to minimise injury to the brain.

Detection of brain injury in the growth restricted newborn. A number of tools currently available may predict long-term neurodevelopmental outcomes in IUGR infants following birth (see Malhotra *et al.* 2013 for further details). Gross measures such as head circumference are a good predictor of outcome, with small head circumference correlating with poor neurodevelopmental outcome (Gale *et al.* 2006). Advanced neuroimaging provides the opportunity to identify and monitor the

progression of brain injury in IUGR newborns. The use of non-invasive *in vivo* techniques, such as magnetic resonance imaging (MRI) and electroencephalography (EEG) hold promise in characterising structural and functional aspects of myelination and connectivity in relation to injury progression, neuroplasticity and repair. Diffusion based MRI techniques such as diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI) will enable more detailed and specific evaluation of white matter microstructure and integrity as well as cortical complexity.

Analysis of umbilical vein blood using nuclear magnetic resonance spectroscopy (MRS) has shown metabolite changes in IUGR infants that may be indicative of brain injury (Sanz-Cortes *et al.* 2013). The presence of proteins such as S-100 β (from astrocytes) or neuron-specific enolase (NSE; from neurons) are considered as evidence that these cells have been damaged, and the proteins are released into the blood through increased permeability of the BBB. Elevated cord blood levels of S100 β and NSE show a relationship with neonatal complications such as mortality and necrotising enterocolitis (NEC) in IUGR newborns (Velipasaoglu *et al.* 2015). While promising, the search for reliable blood biomarkers of brain injury remains ongoing.

Brain injury that follows IUGR is a major cause of morbidity and mortality worldwide but despite this, pharmacological interventions have been insufficiently studied. Antenatal treatment is likely to be beneficial, but the majority of IUGR babies are first diagnosed at or around birth (Sovio *et al.* 2015). The developing brain exhibits plasticity and the potential for regeneration (neurogenesis) following injury. Studies in rodents have shown neurogenesis occurs after stressors or injuries such as seizures, stroke or HI (Kadam *et al.* 2008; Yoo *et al.* 2008; Scharfman & McCloskey, 2009). Even though neurogenesis may be preserved or even increased after an insult, the immature brain has limited capacity to fully regenerate alone (i.e. without treatment) after injury (Donega *et al.* 2013). Postnatal treatments have been shown to induce neuronal regeneration in neonatal HI models (reviewed in Donega *et al.* 2013); therefore it is important to detect growth restriction early to maximise the chance an intervention will have to prevent long-term adverse neurological outcomes.

Treatments in clinical trials for the IUGR fetus and newborn. The importance of timing of delivery, mode of delivery, avoidance of additional HI insult during labour, and minimizing fetal/neonatal inflammation is crucial to the health of the IUGR infant, as all of these factors could exacerbate brain injury. Management options for the IUGR infant are limited to postnatal strategies to reduce neurological deficits and include the Newborn Individualised Developmental and Assessment Program

(NICCAP) (Als *et al.* 2011, 2012; McAnulty *et al.* 2017), but evidence of efficacy is not strong. Other management options are limited. No treatments are currently available to reduce brain injury in the IUGR fetus or newborn, but a number of clinical trials examining the protective effects of therapeutic interventions are underway.

Clinical trials. Most of the current clinical trials are focused towards the improvement in overall growth of IUGR babies. Primary outcomes for clinical trials examining administration of sildenafil citrate, heparin, L-arginine, omega 3, aspirin and diet modification are an increase in fetal weight and/or healthy survival; however, very few of these studies have investigated the effects of these interventions on brain outcomes. Of the few clinical trials to examine neurological outcomes most are as secondary outcome measures.

Antenatal treatments. The STRIDER studies are multiple international clinical trials of sildenafil citrate administration to pregnant mothers in order to improve uteroplacental blood flow. Recent studies have identified that sildenafil citrate results in vasodilatation of small myometrial vessels with associated improvements in amniotic fluid index, uterine and umbilical artery Doppler patterns and fetal weight. A study of 100 pregnant women administered sildenafil citrate showed improvement in perinatal outcome and no long-term adverse effects on the mother or baby as followed up at 3 years (Premalatha *et al.* 2016). The majority of STRIDER clinical trials do not examine neurological outcomes; with the exception of two studies currently recruiting. A STRIDER trial (NCT02277132) recruiting through Universiteit van Amsterdam aims to examine age adequate performance on the 2 year Bayley Scale of Infant and Toddler Development (BSITD-III). Another STRIDER trial recruiting through University of British Columbia (NCT02442492) will examine intact survival without evidence of severe central nervous system injury by either ultrasound or MRI. However, modifications to these trials (or potentially cessation) may be imminent with the recently published outcomes from a STRIDER study in the United Kingdom reporting that sildenafil treatment did not improve survival nor reduce short-term neonatal morbidity; the authors do not recommend prescription of sildenafil for treatment of IUGR (Sharp *et al.* 2018).

The EVERREST Project (doEs Vascular endothelial growth factor gene therapy safely impRove outcome in severe Early-onset fetal growth reSTriction?) (NCT02097667; currently recruiting) is a multicentre clinical trial investigating a treatment designed to increase fetal growth in severe early onset fetal growth restriction. Using an adenoviral vector, maternal vascular endothelial growth factor (VEGF) factor therapy will be delivered to

the pregnant mother's uterine arteries to increase uterine artery blood flow and thus fetal growth. Primary outcomes include growth and neurodevelopment at 2 years of age (Spencer *et al.* 2017). The detailed neurodevelopmental follow-up plan includes: Prechtl video assessment at 3 and 6 months, Hammersmith assessment at 12 and 24 months, BSITD-III at 12 and 24 months, Gross Motor Function Classification Systems (GMFCS) and Manual Ability Classification System (MACS) at 24 months.

A clinical trial titled 'Melatonin to prevent brain injury in unborn growth restricted babies' (NCT01695070; completed) came about from favourable results from animal studies (Miller *et al.* 2014). Even though the running title of the clinical trial mentions the prevention of brain injury, the main aim of the study was the examination of oxidative stress (from umbilical artery). However, one of the secondary outcome measures was to determine abnormal neurological assessment, though specific details are lacking on the exact measures. In the published study protocol for this clinical trial (Alers *et al.* 2013), the authors aim for long-term follow-up using neurodevelopmental examination, questionnaires and MRI, but note this will depend on funding.

Postnatal treatments. A multicentre randomised controlled trial (RCT) (NCT02999945; not yet recruiting) examining nutritional management with enhanced nutrients given fortified breastmilk or formula for 3 months to infants who are SGA or IUGR is aiming to evaluate the difference in metabolic profiles of these groups. Data from discharge to 3 months will include long-term neurodevelopmental outcomes using the BSITD-III at 24 months, body composition, metabolic programming, metabolomics and the microbiome.

Erythropoietin (Epo) has been trialled as a neuro-protectant in extremely low birth weight infants (ELBW, ≤ 1000 g birth weight) (Juul *et al.* 2008; Neubauer *et al.* 2010) (these studies have not yet stratified for IUGR). One study found Epo did not cause excess morbidity or mortality in ELBW infants (Juul *et al.* 2008) and the authors aim to proceed with clinical trials. Only a limited number of ELBW infants have been followed up for long-term neurodevelopmental outcomes but to date there is no indication that Epo has a neuroprotective effect or improves neurodevelopmental outcomes at 18–22 months' corrected age (Ohls *et al.* 2004; Bierer *et al.* 2006). In contrast, a study of 200 ELBW children assessed at 10–13 years of age with an intelligence quotient score demonstrated a neuroprotective effect of Epo treatment administered in the first week of life (Neubauer *et al.* 2010). The variable dosage and timing of Epo treatment may result in these discrepant results. While neuroprotective effects may be apparent, studies in preterm infants demonstrate adverse outcomes of Epo administration such as an

increase in rate of retinopathy of prematurity (ROP) (Ohlsson & Aher, 2012). This Cochrane review concluded from the limited clinical benefits and the increase in ROP that Epo administration is not recommended to preterm or LBW newborns (Ohlsson & Aher, 2012).

Treatments in animal models of IUGR. The use of animal studies allows for detailed examination of neurological outcomes following both maternal antenatal treatment (Liu *et al.* 2011, 2013, 2012; Roman *et al.* 2013; Miller *et al.* 2014; Liu *et al.* 2015a,b; Castillo-Melendez *et al.* 2017; Wang *et al.* 2017), as well as postnatal therapies (Mazur *et al.* 2013; Pham *et al.* 2015) (Fig. 1). The direct effect of several treatments, including those already in clinical trials on neurodevelopment have been studied in detail in IUGR animal models with encouraging results.

Pham *et al.* (2015) demonstrated in antenatal hypoxia-induced IUGR rats that 7 days of low dose (5 ppm) inhaled nitric oxide during the first postnatal week significantly attenuated cell death and microglial activation and improved myelination and cognitive function (Pham *et al.* 2015). Inhaled nitric oxide was associated with upregulation of P27kip1, which initiates oligodendrocyte differentiation.

Epo is known to exert anti-inflammatory effects in the neonatal brain (Feng, 2006) and to reduce inflammatory cytokine production in term and preterm infants (Strunk *et al.* 2008). In the neonatal rat placental insufficiency model, Epo was administered postnatally at three different dosages: low (500 IU kg⁻¹ for 1 day), moderate (1000 IU kg⁻¹ for 3 days), and high (2000 IU kg⁻¹ for 5 days). Only the high-dose regimen was used for adult neurological outcomes. Although inflammatory markers were not directly examined in this study, adult rats showed enhanced oligodendrocyte and neuronal survival, as well as histological improvement (Mazur *et al.* 2013). However, as mentioned previously, proceeding to clinical trials should be considered with caution due to potential adverse effects in preterm infants treated with Epo.

Melatonin is an anti-oxidant which also has anti-inflammatory properties. Melatonin is effective in reducing maternal LPS-induced neonatal brain inflammation and related brain injury (Carloni *et al.* 2016). Preclinical studies of maternal antenatal melatonin administration (intravenous infusion of 0.1 mg kg day⁻¹ from 0.7 gestation until term) in pregnant sheep demonstrated an amelioration of oxidative stress, recovery of disrupted white matter tracts and axonal damage in newborn lambs 24 h after delivery (Miller *et al.* 2014). In the same model melatonin administration reduced BBB disruption by protecting the perivascular cells which are important for maintenance and stability of the neurovascular unit (Castillo-Melendez *et al.* 2017). This study also showed a disruption to astrocyte endfeet attachment

in the white matter of the IUGR lambs, which was normalised with melatonin administration.

Taurine may be a potential neuroprotectant in the IUGR animal model. Taurine is one of the most abundant amino acids in the brain and plays a role in oxidative stress; however, its mechanism of neuroprotectant action is unclear (Ripps & Shen, 2012). Maternal antenatal taurine administration (300 mg kg day⁻¹ from conception until day of birth) improved IUGR fetal brain development in the newborn rat pup, as demonstrated by increasing brain weight, reducing neuronal apoptosis and improving brain ultrastructure (Liu *et al.* 2011, 2013). Maternal antenatal taurine administration also promotes cell proliferation and activation of neurotrophic factors and improves neural stem cell proliferation in the newborn IUGR rat (Liu *et al.* 2012, 2015a,b; Wang *et al.* 2017). Glial fibrillary acidic protein (GFAP)-immunoreactive cells were found to be increased in the IUGR animals with further increases in the taurine-treated groups (Liu *et al.* 2011). The authors speculated that as astrocytes perform an important protective role during brain development, the increased counts of GFAP-immunoreactive cells may have been a compensatory beneficial mechanism that was further enhanced by taurine treatment. However, the morphology of the astrocytes was not examined. Reactive astrocytes, which are identified by short thickened processes, release detrimental proinflammatory cytokines, and thus increased counts may in fact exacerbate neuronal injury.

Even though maternal taurine treatment demonstrated favourable brain outcomes in animal studies (Liu *et al.* 2011, 2013, 2012, 2015a,b; Wang *et al.* 2017), several clinical trials of taurine supplementation have failed to show any positive effect on neurological outcome in LBW infants (Verner *et al.* 2007). The trials of postnatal supplementation of taurine that have shown no benefit compared with the positive effects in animal studies of antenatal supplementation may be due to differences in route of administration or sensitivity of the brain at different stages in development.

Only one of the aforementioned treatments has progressed to clinical trials – melatonin. As melatonin exerts anti-inflammatory effects on the neonatal brain, investigating other treatment options targeting inflammatory mechanisms could provide appealing alternatives.

Ibuprofen. Ibuprofen is an anti-inflammatory drug that is currently safely used in the preterm neonate; it is therefore a potential therapeutic candidate to treat brain injury in the IUGR neonate. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is used widely for its anti-inflammatory, anti-pyretic and analgesic properties. The molecular basis for its therapeutic action is its ability

to inhibit cyclooxygenase (COX) activity and thereby block the production of prostaglandins, which themselves are neuroinflammatory mediators (Lehmann *et al.* 1997; Boje *et al.* 2003) that have been found to be elevated in IUGR infants (McElrath *et al.* 2010). Ibuprofen is a lipophilic compound that readily crosses the BBB following systemic administration (Parepally *et al.* 2006; Kokki *et al.* 2007). Side-effects of ibuprofen administration to the newborn are rare, but include pulmonary hypotension, displacement of bilirubin, transient renal effects and gastrointestinal problems (Gournay *et al.* 2002; Tatli *et al.* 2004; Desfrere *et al.* 2005; Ambat *et al.* 2008). These complications particularly occur when ibuprofen is administered in high doses.

Ibuprofen and cerebral haemodynamics in the preterm brain. Ibuprofen has been shown to be safe and well tolerated in the preterm human neonate and is widely used for treatment of patent ductus arteriosus (PDA) (Ohlsson *et al.* 2015); with fewer adverse side-effects than the previous therapy (indomethacin) (Chemtob *et al.* 1991; Varvarigou *et al.* 1996; Patel *et al.* 2000; Ohlsson *et al.* 2015; Kalani *et al.* 2016). Ibuprofen is administered in relatively low doses in the preterm neonate for PDA, typically 5–20 mg kg day⁻¹ (Ohlsson *et al.* 2015). A prospective study of 96 preterm neonates

showed ibuprofen administration was associated with a reduction of intraventricular haemorrhage (IVH) without any significant side-effects like renal dysfunction, gastrointestinal bleeding or NEC (Kalani *et al.* 2016). One study examined cerebral haemodynamics in preterm infants with PDA and showed that ibuprofen enhanced autoregulation of cerebral blood flow, cerebral blood volume and cerebral oxygen delivery (Patel *et al.* 2000). Abnormalities of cerebral perfusion play an important role in the development of cerebral injury in newborn infants. Therefore ibuprofen administration, which had no adverse effects on cerebral haemodynamics in preterm babies, may represent a favourable drug choice. Studies in newborn piglets show ibuprofen administration enhances cerebral blood flow autoregulation (Chemtob *et al.* 1990), and protects retinal function following neonatal asphyxia (Chemtob *et al.* 1993). Stabilising cerebral blood flow can have many positive consequences on the IUGR neonatal brain such as stabilising cerebral oxygenation; as potentially harmful fluctuations in cerebral oxygenation can result in cellular injury.

Effects of ibuprofen on neuroinflammation in the newborn hypoxic animal model. Although the potential neuroprotective effects of ibuprofen administration have not been examined in animal models of IUGR, there

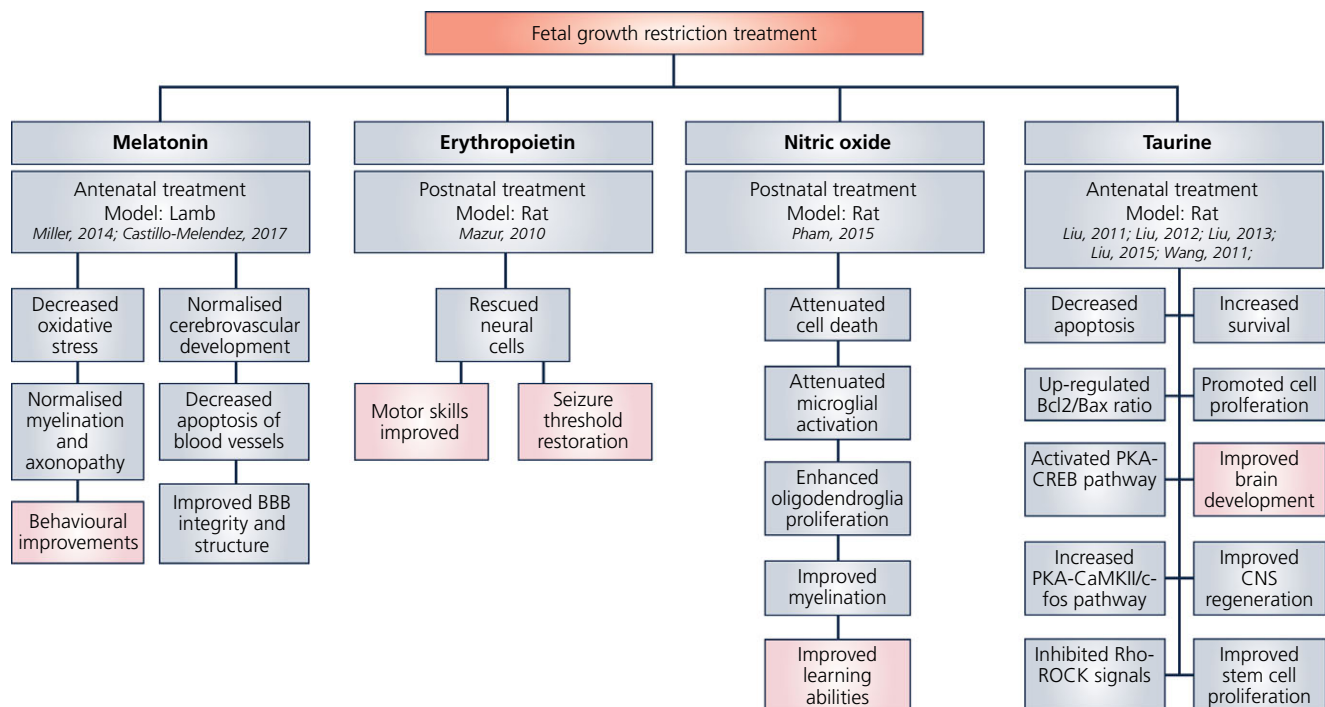


Figure 1. Mechanisms and behavioural outcomes of treatments trialled in IUGR animal models

is evidence from neonatal animal models of acute HI. However, we note acute HI insults at birth and chronic hypoxia in IUGR fetuses resulting in brain injury are different insults which could involve different mechanistic pathways. It is becoming increasingly apparent that systemic ibuprofen inhibits central neuroinflammation and has neuroprotective effects in animal models of neonatal HI (Carty *et al.* 2011; Wixey *et al.* 2012). Ibuprofen treatment attenuates HI-induced increases in COX-2 expression and proinflammatory cytokine levels in the neonatal HI rat brain (Wixey *et al.* 2012). Ibuprofen administration concurrently protects the white matter and neurons in this preterm rat model of HI injury (Carty *et al.* 2011; Wixey *et al.* 2012). The author postulates this is due to ibuprofen's ability to inhibit COX-2 and downstream neuroinflammatory mediators such as prostaglandins and proinflammatory cytokines (Wixey *et al.* 2012). However behavioural tests were lacking in these studies. It would be beneficial to assess whether ibuprofen administration can improve neurobehavioural deficits. Though, there is an emerging role for COX-2 inhibitors to improve behavioural and cognitive functions following neonatal HI and adult ischaemic brain injury in animal models (Candelario-Jalil *et al.* 2004, 2005; Fathali *et al.* 2010). Ibuprofen may be a favourable candidate to reduce brain injury in the IUGR neonatal brain.

Better understanding of when neuronal and white matter injury occurs would assist with determining therapeutic interventional timing. Do we have to treat *in utero* or is there the opportunity to treat postnatally? Preclinical IUGR piglet studies demonstrate that brain injury occurs late in gestation and continues postnatally (Kalanjati *et al.* 2017). The spontaneous/naturally occurring IUGR piglet shows neuronal and white matter injury from 104 days of gestation (term = 115 days) to postnatal day 7, with no significant white matter or neuronal injury detected at 100 days of gestation. As neuroinflammation may play a major role in the progression of this brain injury, this raises the opportunity to reduce the ongoing neuronal and white matter injury by therapeutically targeting inflammation in the IUGR newborn.

Ibuprofen in clinical trials in newborns—neurological outcomes. Very few clinical trials have investigated neurological outcomes in IUGR, preterm or LBW infants following ibuprofen treatment. A study by Schmid (NCT01428180) completed in April 2016 examined PDA treatment (ibuprofen, indomethacin and ligation) effects on cerebral tissue oxygenation, but no study results have been reported. Another interesting RCT (NCT01630278) is currently recruiting for early ibuprofen treatment for PDA in premature infants with 2 year survival without cerebral

palsy as a primary endpoint. A 2015 Cochrane review of 33 studies compared the effectiveness of ibuprofen administration methods and other treatment regimens for PDA, but noted the paucity of long-term neurodevelopmental follow-up data is of concern (Patel *et al.* 2000; Ohlsson *et al.* 2015; Cohen *et al.* 2017). There have only been a handful of studies reporting 18–24 months follow-up data for ibuprofen treatment for PDA (see Table 1). However, only one of these studies reported neurodevelopmental outcomes in ibuprofen-treated infants *vs.* no treatment (Bourgoin *et al.* 2016). In this retrospective study, ibuprofen treatment did not improve 'non-optimal outcome' and there was no difference in mean developmental quotient.

However, a recent retrospective cohort study shows a potential neuroprotective effect of ibuprofen in extremely preterm infants (EPT) (Padilla *et al.* 2015). This study compared MRI brain morphology in EPT infants at term and term-born infants. While all EPT infants have significant global reduction in cortical and subcortical grey matter, the EPT infants treated with ibuprofen for PDA had preserved brain volumes compared to those who had not received ibuprofen.

Conclusion

The life-long neurodevelopmental disabilities that occur in some IUGR infants place considerable burden on the individual, their family, the health system and societal resources. Clinical trials are underway to test interventions to improve outcomes in the IUGR newborn. It is vitally important to incorporate brain outcomes into the studies; as protecting the brain is critical to improve neurodevelopmental outcomes. The recently announced Cosgrove project (Core Outcome Set for GROwth restriction: developing Endpoints) does aim to identify both a core outcome set to be measured in future studies on pregnancies complicated by fetal growth restriction and to improve reporting on meaningful neurodevelopmental outcomes. At the moment, different studies into the prevention or treatment of fetal growth restriction measure different outcomes in different ways, which makes comparison or structured analysis problematic.

The development of therapies in fetal IUGR and neonatal brain injury has been identified as warranting urgent research for several years, but few trials have been reported. To better understand the potential of ibuprofen and other agents to be neuroprotective in the IUGR neonate, long-term follow-up information of neurodevelopmental outcomes must be studied. Where agents such as ibuprofen are shown to be effective, have a good safety profile and are relatively inexpensive, they can be widely adopted and lead to improved outcomes.

Table 1. Ibuprofen administration to newborns with patent ductus arteriosus – neurodevelopmental outcomes

Treatment comparison	Number of participants	Study type	Time frame	Neurodevelopmental outcomes	Other outcomes
<ul style="list-style-type: none"> • Oral ibuprofen • Intravenous ibuprofen (Eras, 2013) 	<ul style="list-style-type: none"> • N = 30 • N = 27 	Randomised controlled trial	18–24 months corrected age	<ul style="list-style-type: none"> • Oral and i.v. ibuprofen treatment had similar neurological, neurosensory, and cognitive outcomes at 2 years of age. • No comparison between treatment and no treatment. 	No vision or hearing impairment noted for both ibuprofen groups.
<ul style="list-style-type: none"> • Ibuprofen • Paracetamol (Oncel, 2017) 	<ul style="list-style-type: none"> • N = 31 • N = 30 	Randomised controlled trial	18–24 months corrected age	<ul style="list-style-type: none"> • No significant difference in neurodevelopmental outcomes between paracetamol and ibuprofen treatment. • No comparison between treatment and no treatment. 	Blindness and deafness observed in 1 of the ibuprofen treated newborns.
<ul style="list-style-type: none"> • Ibuprofen • Indomethacin (Rheinlander, 2010) 	<ul style="list-style-type: none"> • N = 70 • N = 71 	Retrospective	24 months	<ul style="list-style-type: none"> • No difference in neurodevelopmental outcomes at 24 months between treatment groups. • No comparison between treatment and no treatment. 	No difference in hearing or vision impairment between indomethacin and ibuprofen groups.
<ul style="list-style-type: none"> • Ibuprofen • Surgical ligation • No treatment (Bourgoin, 2016) 	<ul style="list-style-type: none"> • N = 248 • N = 104 • N = 505 	Retrospective	24 months	<ul style="list-style-type: none"> • Ibuprofen treatment did not improve 'nonoptimal outcome' at 24 months in comparison to no treatment. • Surgical ligation significantly correlated with neurodevelopmental impairment at 24 months. 	NB. Children with non-optimal neuromotor and/or psychomotor assessments were regarded as having an overall 'non-optimal neurodevelopmental outcome'.
<ul style="list-style-type: none"> • Medical management (ibuprofen/indomethacin) • Surgical ligation (Weisz, 2017) 	<ul style="list-style-type: none"> • N = 570 • N = 184 	Retrospective	18–24 months corrected age	<ul style="list-style-type: none"> • No difference in neurodevelopmental impairment between surgical ligation and medical treatment in adjusted model. 	In unadjusted model there was a statistically significant increased risk of moderate-severe neurodevelopmental impairment, chronic lung disease and retinopathy of prematurity

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Additional information

Competing interests

None of the authors have any conflicts of interest.

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