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REVIEW ARTICLE

Early closure mechanisms of the ductus arteriosus in immature infants

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Abstract

Aim: According to experimental studies, cardiopulmonary distress decreases after closure of patent ductus arteriosus. However, early closure of the ductus using ibuprofen or indomethacin has failed to increase survival without serious morbidity. We review relevant data aiming to define optimal early management strategies that promote early closure of ductus arteriosus without serious adverse effects.

Methods: Literature in English was searched selectively focusing on the potential of using acetaminophen for early closure of the ductus.

Results: Prophylactic ibuprofen or indomethacin intended to close the ductus, predisposes infants to ischaemia, bleeding and immune dysfunction. Acetaminophen appears to have a similar efficacy as indomethacin or ibuprofen, and all three dose-dependently constrict the ductus. Ibuprofen and indomethacin cause non-specific inhibition of prostaglandin synthesis, while acetaminophen predominantly inhibits prostaglandin E synthesis. Owing to low CYP450 activity in infancy, acetaminophen toxicity has been rarely evident. However, increasing the dosage increases the oxidative stress. We review prophylactic treatments that may increase the safety and efficacy of acetaminophen. These include vitamin A, cysteine and glutamine, and low-dose corticosteroid supplementation.

Conclusion: The current challenge is to define a safe perinatal management practice that promotes cardiorespiratory adaptation in immature infants, particularly the seamless closure of the ductus before significant cardiopulmonary distress develops.

KEYWORDS
patent ductus arteriosus, acetaminophen, indomethacin, ibuprofen, extremely premature neonate

Key notes

- It is unclear whether early medical closure of patent ductus arteriosus (PDA) improves the outcome of immature infants.

Abbreviations: AA, acetaminophen (paracetamol); ADHD, attention-deficit/hyperactivity disorder; BPD, bronchopulmonary dysplasia; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; CYP, cytochrome P450; ELGA, extremely low gestational age (<28 weeks); GSH, reduced glutathione; IVH, intraventricular haemorrhage; NAC, N-acetyl cysteine; NAPQUI, N-acetyl-*p*-benzoquinone imine; NEC, necrotising enterocolitis; NO, nitric oxide; NSAID, Non-steroidal anti-inflammatory drug; PDA, Patent ductus arteriosus; PG, prostaglandin; PGI, prostacyclin; POX, peroxidase; RA, retinoic acid; SMC, smooth muscle cell; Tx, thromboxane; VLGA, very low gestational age (<32 weeks.

- Efficacy and safety of early medical closure of PDA may be improved via choice of drug, its most efficacious dosage and timing of administration.
- Antenatal therapies that may promote early PDA closure in immature infants are insufficiently studied, and postnatal timing of initiation of therapy has yet to be determined.

1 | INTRODUCTION

In healthy term-born infants, the ductus arteriosus contracts within two days after birth and the structural transformation to the ductus ligamentum proceeds in the following weeks. The incidence of haemodynamically significant patent ductus arteriosus (PDA) increases as a function of the degree of prematurity.[1] The ductus is still open at 4–7 days of age in 2%–10% of infants born at 30–36 weeks of gestation, whereas in infants born at 24–26 weeks, it remains open at 4–7 days of age in 68%–92% of cases.[2] Pulmonary congestion and cardiopulmonary distress accompany an open ductus.[3] The PDA shunt decreases systemic cardiac output and perturbs CNS blood flow. The proposed consequences include bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) or adverse neurological outcome.[4-6]

Experimental evidence indicates that PDA closure improves the alveolar growth,[7] and according to clinical cohort studies, early closure of PDA is beneficial.[8] However, according to the results of meta-analyses of randomised trials, the treatment of PDA has not improved the outcome.[5,6] Ibuprofen and indomethacin are currently labelled for the treatment of PDA. They are non-steroidal anti-inflammatory drugs (NSAIDs). More recently, acetaminophen (AA) has been studied for the same indication. Indomethacin, ibuprofen and AA inhibit the synthesis of prostaglandins (PGs), and this property leads to the contraction of PDA in premature infants.

The disappointing results of early treatment of PDA have led to a shift in the treatment practice towards later and selective PDA closure. Besides the conventional management practices, steroids, non-invasive ventilation practices and caffeine treatment of small preterm infants have decreased the risk of haemodynamically significant PDA.[9]

In this review, the discussion is focused on the mechanisms and strategies aiming to effective and safe PDA closure within less than one week after birth.

2 | REVIEW OF TRIALS OF MEDICAL CLOSURE OF PDA

In 1976, Friedman[10] and Heymann[11] reported on medical closure of PDA using indomethacin. An early controlled trial was focused on the administration of indomethacin in respiratory distress syndrome,[12] and observational studies were carried out, focused on PDA and respiratory distress.[13] The side effects of indomethacin, oliguria and acute ischaemia were at times serious, leading to a search for other inhibitors of prostaglandin synthesis. In the nineties, the first studies on ibuprofen for PDA closure were reported.[5,14] Unlike indomethacin,[14,15] ibuprofen did not decrease cerebral perfusion and ibuprofen was associated with less risk of renal insufficiency than indomethacin.[5,6] Both indomethacin and ibuprofen are currently the labelled drugs for PDA closure.

In 2011, Hammerman[16] described successful AA-induced PDA closure in five premature infants with either a contraindication to or failure of NSAID treatment. Several small trials and cohort studies concerning the efficacy and safety of AA have since been published.[17] Although NSAIDs and AA have functional similarities, they differ in the mechanisms of action, and these differences may have therapeutic consequences.

2.1 | Representative meta-analyses concerning the efficacy and safety of NSAIDs and AA

According to the results of meta-analyses, indomethacin, ibuprofen and AA appear equally effective.[5,6,17] Paired comparisons between AA, indomethacin and ibuprofen revealed no difference in PDA closure rates (Table 1A; many oral drug trials not shown). A recent non-inferiority trial in which oral AA and ibuprofen were compared confirmed the result.[18] In placebo-controlled trials, NSAIDs increased the PDA closure and AA showed a similar trend (Table 1B). The incidence rates of BPD, IVH, NEC, retinopathy of prematurity and neurological outcomes were not affected by any of the drugs.[5,6,17] A higher oral ibuprofen dose was associated with an increase in PDA closure rate in comparison with standard doses of intravenous ibuprofen or indomethacin.[19]

For AA, no adverse effects were reported, and it was associated with a lower risk of oliguria, lower creatinine concentration and higher platelet counts than NSAIDs (Table 1). No significant differences between the treatment groups were reported in long-term follow-up.[5,6,17,19] As a result of the small sample sizes of trials involving AA, more studies, including pharmacodynamic studies, are required. Indeed, a phase III multicentre randomised trial on prophylactic AA (TREOCAPA) has recently started.[20] It also includes an open, phase II dose-response study.

3 | EARLY CLOSURE OF PDA

3.1 | Current recommendations and controversies

Prophylactic treatment of PDA shortly after birth is not recommended, because spontaneous closures are common and there is no evidence of long-term benefit.[9] In one study, early

TABLE 1 Closure of PDA and major neonatal outcomes: Comparison of acetaminophen, ibuprofen and indomethacin

A. Comparison of two drugs			
Outcome	**AA vs ibuprofen (oral or iv)**	**AA (oral or iv) vs indomethacin (iv)**	**Ibuprofen vs indomethacin (oral or iv)**
Failure of PDA closure *N* cases + controls	0.95 (0.75–1.21) N 282 + 277	0.96 (0.55–1.65) N 136 + 137	1.07 (0.92–1.24) N 812 + 778
Mortality *N* cases + controls	0.96 (0.55–1.67) N 138 + 134	1.03 (0.43–2.46) N 38 + 39	0.79 (0.54–1.17) N 362 + 335
IVH (Gr 3–4) *N* cases + controls	1.00 (0.30–3.37) N 130 + 134	3.08 (0.34–28.30) N 37 + 38	1.05 (0.68–1.63) N 411 + 387
Necrotising enterocolitis	0.88 (0.46–1.70) N 282 + 277	0.39 (0.14–1.06) N 138 + 139	0.68 (0.49–0.94)[a] N 660 + 632
Gastrointestinal bleeding *N* cases + controls	0.28 (0.12–0.69)[a] N 269 + 268	0.66 (0.33–1.33) N 138 + 139	0.94 (0.55–1.61) N 260 + 254
ROP *N* cases + controls	0.71 (0.41–1.23) N 238 + 234	0.77 (0.58–1.03) N 129 + 120	0.81 (0.61–1.10) N 291 + 290
Sepsis *N* cases + controls	0.88 (0.64–1.21) N 238 + 234	1.14 (0.59–2.19) N 138 + 139	1.22 (0.84–1.76) N 375 + 360
Oliguria *N* cases + controls	0.46 (0.20–1.10) N 169 + 168	[b]	0.28 (0.14–0.54)[a] N 294 + 282
BPD *N* cases + controls	0.87 (0.39–1.95) N 137 + 132	0.93 (0.32–2.69) N 27 + 30	1.12 (0.77–1.22) N 186 + 171
B. Outcomes of trials comparing the drug and placebo			
Outcome	**AA (oral or iv) vs placebo (no or iv)**	**Ibuprofen (iv) vs placebo**	**Indomethacin (iv) vs placebo**
Failure of PDA closure *N* cases + controls	0.49 (0.24–1.0)[a] N 39 + 41	0.71 (0.51–0.99)[a] N 67 + 68	0.44 (0.38–0.50)[a] N 1093 + 1100
Mortality *N* cases + controls	0.35 (0.04–3.2) N 39 + 41	0.58 (0.38–0.89)[a] N 68 + 68	0.82 (0.65–1.03) N 771 + 796
IVH (Gr 3–4) *N* cases + controls	1.09 (0.07–16.39) N 23 + 25	1.00 (0.47–2.15) N 67 + 67	0.66 (0.53 –0.82)[a] N 1285 + 1303
NEC *N* cases + controls	0.36 (0.02–8.45) N 23 + 25	1.84 (0.87–3.90) N 132 + 132	1.09 (0.82–1.46) N 1187 + 1214
ROP *N* cases + controls	3.25 (0.14–76.01) N 23 + 25	1.19 (0.88–1.62) N 65 + 64	1.02 (0.92–1.12) N 784 + 787
Oliguria *N* cases + controls	0.78 (0.29–2.11) N 23 + 25	3.57 (2.56–5.88)[c] N 67 + 67	1.90 (1.45–2.47)[c] N 1045 + 1070
BPD *N* cases + controls	0.36 (0.02–8.45) N 23 + 25	0.99 (0.88–1.11) N 46 + 52	1.06 (0.92–1.22) N 496 + 503

Note: The results shown have been extracted from the meta-analyses of randomised trials.[5,6,17] Risk ratios (95% confidence intervals) and numbers of infants (*N*) are shown. Platelet count higher in AA group vs ibuprofen group (mean difference: 30.2 [16.6, 43.8]).

Abbreviations: AA, acetaminophen; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

[a]Significant decrease in the risk vs the comparison group. For AA vs placebo, PDA closure was significant for the risk difference: −0.21 (−0.41−−0.02).

[b]Serum creatine lower in AA vs indomethacin group (mean difference: −30.9 μmol/L; 95% CI: −34.3−−27.5); daily urine output higher in AA vs indomethacin group (mean difference: 1.14 ml/kg/h; 95% CI: 1.04–1.24).

[c]Significant increase in the risk vs the comparison group.

echocardiography-targeted treatment reduced pulmonary haemorrhage but did not decrease other severe morbidities or mortality.[21] In another study, an expectant management practice was proposed, since PDA eventually closed spontaneously in 73% of infants born before 28 weeks.[22] Statistically significant associations between PDA and poor outcomes and with very early postnatal haemodynamic stress suggest that targeting to very early postnatal PDA closure may optimise the result, but reluctance to test treatment against no treatment is obvious.[23] Others point out that given this lack of important outcomes in randomised trials, there is doubt as to whether closure of the ductus is of benefit at all.[24] Nevertheless, the results of two observational studies suggested that ignorance of PDA during the first days of life was associated with increases in mortality or morbidity. In a single-centre descriptive study, it was pointed out that early prophylactic indomethacin treatment may have the additional benefit of reducing

the incidence of BPD and BPD/death compared with delayed conservative PDA management.[8] In a prospective population-based cohort of extremely preterm infants, screening echocardiography before day 3 of extrauterine life was associated with more treatment of PDA, a lower in-hospital mortality and less pulmonary haemorrhage, but no differences in NEC, BPD or severe cerebral lesions.[25] After more than 40 years of challenges, the management of the preterm PDA remains a conundrum because of the inevitable side effects.

3.2 | Other considerations for early closure of PDA

3.2.1 | Prophylactic AA after very premature birth

Acetaminophen has been given for the treatment of pain and discomfort shortly after very premature birth.[26] Emerging evidence concerning AA-induced closure of PDA [16,17,19] gave an indication for a trial of prophylactic AA against placebo. A phase II placebo-controlled blinded trial of AA (loading 20 mg/kg iv; maintenance 7.5 mg/kg × 4 for 4 days) given to very premature (VLGA: gestation <32 weeks) infants, starting within 24 hours after birth, accelerated PDA contraction and closure, promoted cardiopulmonary stability and had no detectable adverse acute or long-term effects.[27,28]

3.2.2 | Difference in the effects of NSAIDs and AA in imminent very preterm birth

As PGE effectively induces labour and abortion, an inhibitor of PG synthesis was considered as tocolytic agent. Indomethacin was indeed an effective delaying spontaneous premature labour. However, it also constricted PDA in significant proportion of very preterm foetuses[29] and caused oligohydramnios. An antenatal NSAID was also associated with risk of IVH, NEC, periventricular leukomalacia and BPD in VLGA infants.[30]

In a similar way to indomethacin, AA enters the foetal compartment from the maternal side.[31] In contrast, AA neither delayed labour nor constricted foetal PDA before 32 weeks of gestation.[32] According to the results of a retrospective cohort study of 288 foetuses born VLGA, AA treatment shortly before birth was not associated with adverse neonatal effects.[33] However, other cohort studies have shown that the use of AA during pregnancy may be associated with adverse long-term effects in the offspring, including asthma, allergies, autism and attention-deficit/hyperactivity disorder (ADHD).[34,35] These preliminary results are disturbing.

3.2.3 | Early surgery or transcatheter device for PDA closure

Patent ductus arteriosus ligation is associated with excess deaths, IVH, BPD and poor neurodevelopment.[36,37] Intravascular devices inserted by percutaneous catheterisation are associated with bleeding, misplacement and reopening.[38,39] The use of transcatheter devices applied to infants weighing >0.9 kg and postmenstrual age of >29 weeks has been successful [39] but is probably not suitable for early treatment.

4 | DEVELOPMENT OF THE DUCTUS ARTERIOSUS AND REGULATION OF ITS CLOSURE

4.1 | Anatomical development

In the embryo, the ductus arteriosus develops from the neural crest cells within the sixth left aortic arch.[39,40] The muscular layer starts developing early and the wall of the duct is less elastic than that of the aorta. In mid-gestation, the PDA carries 85%–92% of the total right ventricular output and 55%–65% of total cardiac output.[41] At term, the ductus arteriosus carries 70%–75% of right ventricular output and 35%–40% of total cardiac output. In the immature foetus, the PDA wall consists of endothelium, basement membrane and a muscular layer[42] (Figure 1A). Towards the term, the outer muscular layer of the PDA becomes more vascularised and the space between the endothelium and the basement membrane expands, forming a cushion that contains smooth muscle cells (SMCs) from the outer SMC layer.[40] Several agonists, including nitric oxide (NO), contribute to migration of SMCs into the intima. Prostaglandin E_2 stimulates the secretion of hyaluronic acid (HA), the major extracellular constituent of the intima cushion that facilitates PDA closure.[42] For further data, the reader is referred to other articles.[43,44]

4.2 | Mediators of PDA closure

The increase in O_2 saturation shortly after term birth is the major trigger of PDA contraction. The increase in O_2 tension in mitochondrial electron transport complex IV generates peroxide, leading to the activation of the Rho kinase pathway and SMC contraction[45] (Table 2). The increase in O_2 tension also promotes the role of retinoic acid (RA) in PDA contraction.[43] Oxygen further stimulates the interaction between endothelial CYP450 and endothelin-1 (ET-1), which augments PDA contraction[46] (Table 2).

In immature infants, a deficiency in the space-occupying intima cushion, a relatively small and less well-vascularised SMC vascular ring, a lower level of Ca^{2+} channel expression and lower responsiveness to the increase in O_2 saturation hinder or delay the PDA constriction.[47,48]

Prostaglandin E_2 binds to the transmembrane of EP receptors in PDA-SMCs, relaxing them (Table 2). Umbilical vein PGE_2 levels increase towards term as the PGE_2 content of the placenta increases.[49] Soon after term birth, the levels of PGE_2 decrease and inactivation of EP_4 receptors reinforces O_2-induced SMC contraction.[46] After very preterm birth, serum PGE_2 levels barely decrease. Persistent activation

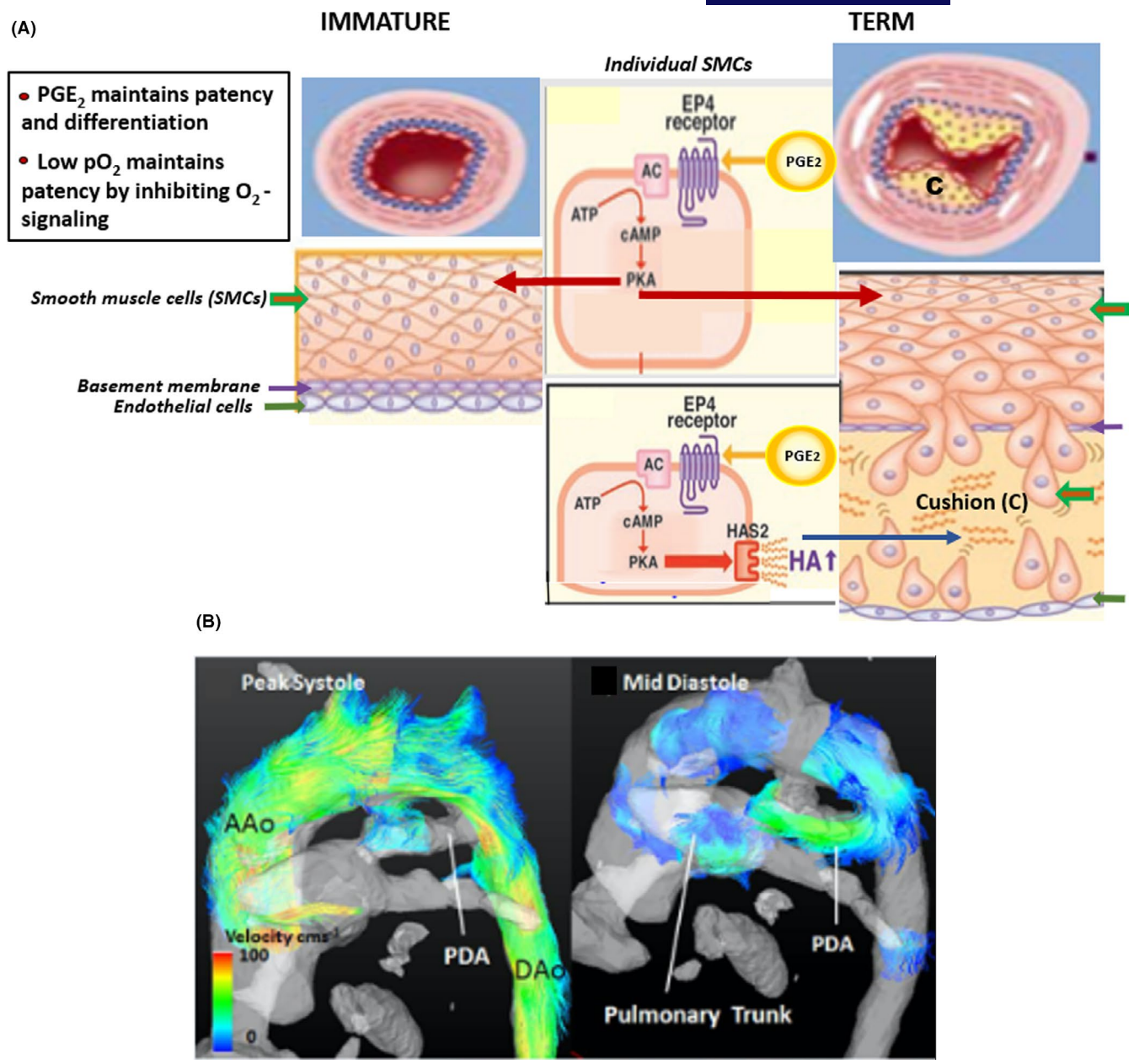

FIGURE 1 Patent ductus arteriosus (PDA) development in the foetus (A) and visualisation of magnetic resonance (MR) velocity data of the PDA and adjacent vessels (B). (A) Development of the ductus arteriosus. Smooth muscle cells (SMCs) pass through the basement membrane towards endothelium. PGE_2 signalling promotes hyaluronic acid (HA) formation within the developing endothelial cushion, forming mature PDA that is narrowed and readily contracted upon the increase in O_2 tension. Immature PDA has a proportionally large lumen and deficient endothelial cushion. Modified from an article by Yokoyama et al.[42] (B) Visualisation of the ductal shunt by 3-dimensional MRI velocity data. PDA and thoracic vessels from a very premature infant are depicted during systole (left) and diastole (right). Note that the flow rates within the vasculature (ranging from 0 to 100 cm/sec) are shown without indicating the direction of flow. Modified from an article by Broadhouse et al[41]

of EP receptors and poor responsiveness of the PDA to an increase in oxygen tension are major causes of PDA in preterm infants.[48]

Activated platelets adhere to the lumen, and localised thrombosis contributes to the persistence of PDA constriction in mice.[44,50] Platelet-derived thromboxane A_2 (TxA_2) and to some extent its hydrolysis product of TxB_2 promote PDA contraction, platelet aggregation and clot formation within the lumen of the ductus arteriosus.[50] Thereafter, in the constricted ductal space, specific growth factors regulate the transformation of the ductus by fibrosis, apoptosis and proliferation, leading to the formation of the ductus ligamentum within 6–8 weeks.[51] In VLGA infants, a deficient PDA vascular ring and a cytokine storm are likely to interfere with constriction and induce mediators promoting PDA reopening (5 to 25% of constricted PDAs).[52]

In vascular endothelium shortly after birth, the synthesis of prostacyclin (PGI) increases and the quantity of its inactive metabolite,

TABLE 2 Factors influencing the contraction and patency of the ductus arteriosus (PDA) in immature and term-born infants

PDA contraction	Immature	Term	References
O_2-tension ↑ a. Mitochondrial H_2O_2 → K_V-channel ↓: PDA-SMC contraction (PSC) b. K^+-channel ↓: O_2 and RA enhance PSC c. CYP450^{3A13} → ET1↑ → PSC	Transiently low O_2 saturation Low O_2 responsiveness Low RA Low CYP450	Increase in O_2 saturation within minutes after birth	Kajimoto[45] Hung[44] Coceani[46]
Glutamate ↑ GluR1 receptor →noradrenaline → PSC	Serum glutamine decreases after birth		Fujita[59]
Low osmolarity →TRPM3 receptor ↑ → intracellular Ca^{2+} ↑ → PSC	Change in osmolarity common		Aoki[60]
Low BNP (cGMP ↓) → PSC	BNP associates with PDA risk		Khosroshahi[62]
Bradykinin →B1 receptor →PSC			Bateson[54]
Glucocorticoid (GC) activity ↑. Additive with PG synthesis inhibitors	PDA risk ↓. Both antenatal and neonatal GC effective		Clyman[67] Hung[44]
Platelet adhesion a. PDA constriction (TxA_2) b. Intra-lumen clot; thrombosis	NSAIDs ↓, AA ~ Low platelets ↓		Seidl[50]
Structural maturity of PDA	Immaturity: thin SMC layer, lack of media cushion	Robust SMCs Cushion	Rabinovitch[40] Yokoyama[42]
Transformation of constricted PDA to PDA ligament	Cushion grows after birth PDA reopening rate 5 to 20%	Defects very rare	Clyman[51]
PDA patency	**Immature**	**Term**	
PGE_2 → EP_4 receptor→AC → cAMP →PKA → dilates PDA-SMC (PSD)	s-PGE_2 from placenta ↓ Inflammation↑, NSAIDs ↓, AA ↓	Elimination of placenta PGE_2 ↓	Coceani[46]
PGI ↑→ IP receptor →cAMP → PSD	Hypoxia, inflammation ↑	Transient ↑	Kluckow[53]
Generalised inflammation: endotoxins, IL–1, TNF-α, free radicals, PGs →PSD	Prevention: non-invasive management, steroids	Endogenous defence	Marseglia[87]
Gasotransmitters have complex roles in vasoregulation. They may affect PDA: 1. NO: cGMP →PSD 2. H_2S: K^+ IC transport ↑ → PSD 3. CO: ET1↓ → PSD	NO synthase upregulated in inflammation: inhaled NO barely reaches PDA tissue H_2S: produced in S metabolism CO: haem oxygenase product	Transient ↑	Hung[44] Baragatti[56] Coceani[55]
Other drugs: PDE5 inhibitors; Mg^{++}; sedative analgesics; histamine antagonists; gentamicin; others	Some drugs either delay contraction of PDA potentially associate with PDA		Reese[57]

Abbreviations: AC, adenyl cyclase; B1 receptor, bradykinin receptor; BNP, B-type natriuretic peptide; cAMP; cGMP, cyclic guanosine monophosphate; cyclic adenosine monophosphate; ET1, endothelin; GC, glucocorticoid; H2, histamine receptor; IC, intracellular; IP, prostacyclin receptor; PDE5, cGMP-specific phosphodiesterase type 5; PGI, prostacyclin; PKA, protein kinase A; PKG, protein kinase G; PSC, PDA-SMC contraction; PSD, PDA-SMC dilatation; RA, retinoic acid; SMC, smooth muscle cells; SMCs, smooth muscle cells; TxA2, thromboxane; TM, transmembrane; TRPM3, transient receptor potential melastatin 3.

6-keto-$PGF_{1\alpha}$, is associated with PDA.[53] PGI_2 dilates PDA-SMCs.[44] Since PGI_2 is rapidly degraded locally, its role in PDA is likely to be limited. An increase in bradykinin at birth activates its B1 receptors, and this may lead to PDA contraction.[54]

Nitric oxide, carbon monoxide (CO) and hydrogen sulphide (H_2S) dilate PDA-SMCs[43,55,56] (Table 2). Inhaled NO enhances the left-to-right shunt through the PDA. It is used in the treatment of hypoxic persistence of the foetal circulation in VLGA infants. Cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase-5 inhibitors generate NO and dilate PDA-SMCs.[57] Carbon monoxide is a catabolism product of Hb that relaxes SMCs,[56] and a high level of CO in exhaled air is associated with PDA.[58] In severe inflammation, high quantities of NO, CO or H_2S may be generated, and these toxic gases inhibit mitochondrial electron transport.[44,56]

Glutamate activates GluR1 receptors, and it stimulates PDA contraction.[59] The activation of TRPM3 receptors triggered by hypo-osmolarity constricts the PDA.[60] Cardiac natriuretic peptides mediate their effects through the generation of intracellular cGMP.[61,62] $MgSO_4$ infusion in cases of threatened preterm birth may considerably increase Mg^{++} levels, which are associated with PDA.[58] Caffeine has been reported to decrease the incidence of PDA.[63] However, it did not contract premature sheep PDA.[64] Therefore, the decrease in PDA risk may be a consequence of decreased severity of respiratory distress. Antenatal and early neonatal corticosteroid treatments decrease the risk of PDA.[65,66] Glucocorticoid influences PDA closure by multiple mechanisms[43,67] (Table 2). Other drug effects on PDA have been reported as well.[58]

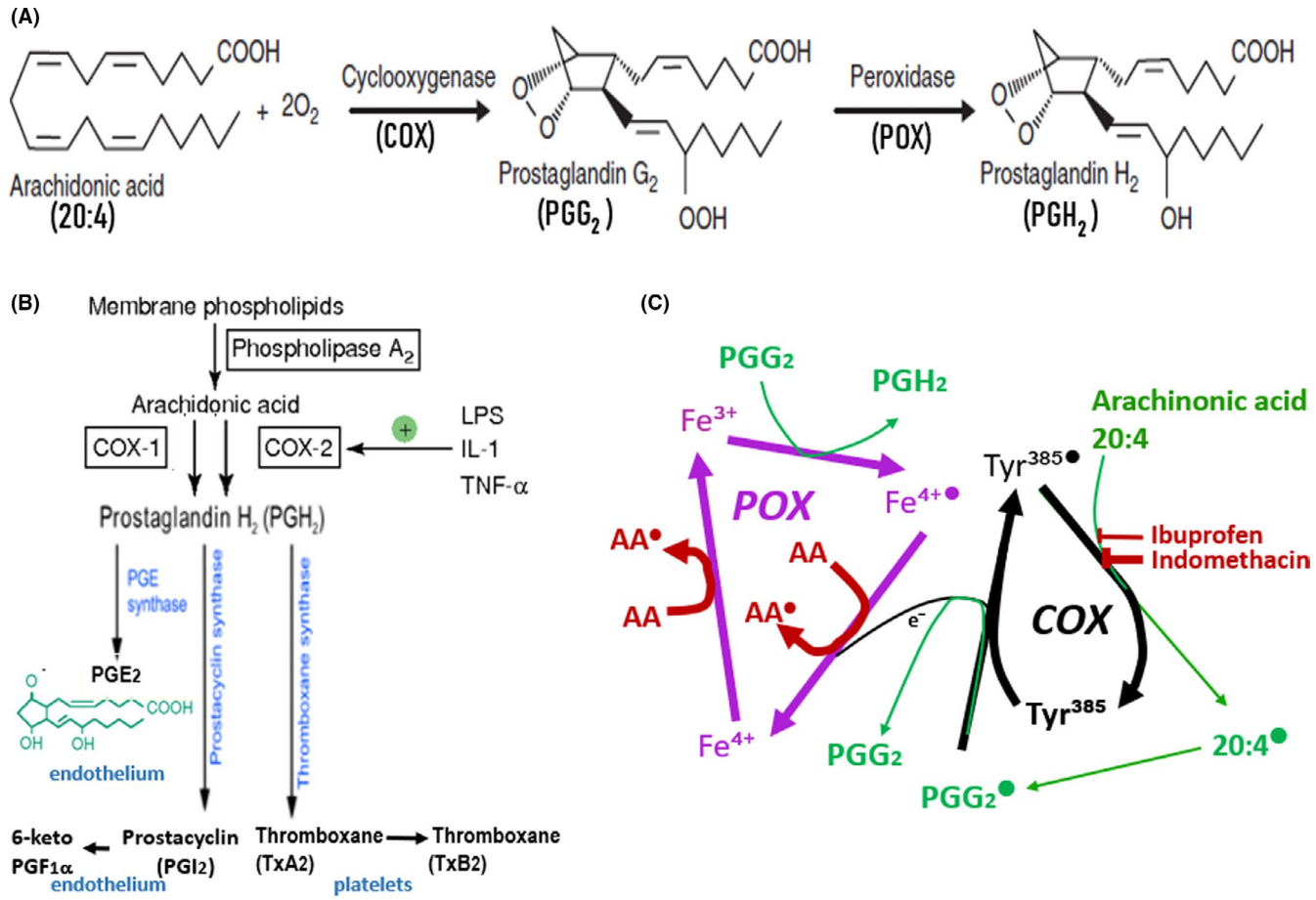

FIGURE 2 Synthesis of the prostaglandins that influence PDA contraction and the action of inhibitors of prostaglandin synthesis. (A) Synthesis of the common PG precursor, PGH_2, from arachidonic acid. (B) Synthesis of prostaglandins from membrane phospholipids. PGE_2, TxA_2 and PGI_2, relevant to the present discussion, are shown. (C) Schematic presentation of the function of cyclooxygenase (COX) and peroxidase (POX) activities, as well as the site of action of inhibitors of PG synthesis. Note that AA serves as a reducing agent, decreasing oxidised ferryl protoporphyrin ($Fe^{4+\bullet}$), available for the activation of Tyr^{385} in COX enzyme

Early PDA closure soon after extremely short gestation may be a result of genetic resilience.[68] Genetic studies on PDA susceptibility are likely to lead to the identification of genes and pathways that influence spontaneous or drug-induced PDA closure; these observations could eventually contribute to the development of new therapies.[69]

5 | PROSTAGLANDIN SYNTHESIS AND ITS INHIBITION

The prostaglandin (PG) precursor arachidonic acid originates from membrane phospholipids. The enzyme complex providing the substrate for specific PG synthases contains cyclooxygenase (COX) and peroxidase (POX) (Figure 2A). There are at least two cyclooxygenase isomers, COX1 and COX2. The latter is mostly inducible by inflammatory mediators, whereas COX1 is mostly constitutional. Despite the differences in localisation and regulation of activity, their mechanism of action is similar.[70] All specific PG synthases utilise PGH_2 as the substrate (Figure 2B). PGE_2 is the main endogenous PGE that maintains PDA.

The function of COX and POX enzymes is sketched in Figure 2C. The POX-associated ferryl$^{(4+)}$ protoporphyrin IX radical generates the tyrosine (Tyr^{385}) radical of the COX enzyme.[71] The Tyr radical further activates arachidonic acid for the formation of PGG_2. The POX enzyme catalyses the reduction of PGG_2 to PGH_2 and additionally regenerates the ferryl$^{(4+)}$ protoporphyrin IX radical.

5.1 | Mechanisms of prostaglandin synthesis inhibitors

Ibuprofen binds transiently to COX, whereas indomethacin shows more prolonged binding and more persistent inhibition of COX activity. Inhibition of all specific PG synthases increases as a function of ibuprofen or indomethacin concentration.[72] NSAID-induced inhibition of PG synthesis inhibits SMC relaxation, immune reactions and blood clotting, and contributes to ischaemia, intestinal perforations

and bleeding disorders.[6] Inhibition of COX activity additionally influences the lipoxygenase pathway and hydroxy fatty acid synthesis, utilising arachidonic acid as precursor.[73]

Acetaminophen inactivates the ferryl$^{(4+)}$-protoporphyrin IX radical cation of POX, thereby inhibiting the COX activity (Figure 2C). AA serves as a reducing agent, while it is oxidised to the AA radical (AA•).[71,74] The apparent selectivity of AA as a PGE_2 synthesis inhibitor is based on the results of observational studies: PG synthase destined to PGE_2 synthesis is dose-dependently inhibited by AA, because it is associated with low activities of COX and POX activities and low substrate levels (20:4 and H_2O_2).[71] PG synthases destined to PGI_2 or to TxA_2 are associated with high COX activities, and AA fails to dose-dependently inhibit these activities.[74]

In the central nervous system (CNS), COX2 inhibition by AA is associated with analgesia and a decrease in fever during acute infection.[74] The analgesic effect AA is also a result of stimulation of the endocannabinoid receptor by a mechanism different from PG synthesis.[73] AA further inhibits the activity of another haem-containing peroxidase and myeloperoxidase from granulocytes; it catalyses the formation of hypochlorous acid and protein-associated tyrosyl radicals.[74] Serum myeloperoxidase is associated with the risk of PDA.[75]

Acetaminophen toxicity is associated with the accumulation of the AA oxidisation product N-acetyl-*p*-benzoquinone imine (NAPQUI) in the liver.[76] The formation and elimination of this serious hepatic and neurotoxin are briefly described in Figure 3.

6 | EARLY PHARMACOLOGICAL PDA CLOSURE IN IMMATURE INFANTS

6.1 | Pharmacodynamics of AA

According to current knowledge, AA may be as effective as NSAIDs in PDA closure and the safety record of AA is better.[19] The calculated mean clearance rate following a treatment dose of AA to neonates born at an extremely low gestational age (ELGA, ie <28 weeks of gestation) was 0.135 L/kg/h (SE 3.9%).[77] It gradually increased with gestation, and by 44 weeks post-conception, the mean clearance rate was 0.17 L/kg/h.[77,78] Intravenous (iv) AA, administered as a slow infusion, is the preferred route in immature neonates shortly after birth.[27,77] Enteral AA, with similar bioavailability and more gradual uptake, is also used,[18] but rectal AA shows low and unpredictable bioavailability. In ELGA infants, AA is nearly exclusively conjugated to sulphate[77] (Figures 3 and 4). Glucuronidation of AA increases during gestation, being ~20% at term, and it increases further in infancy and childhood.[77-79]

Maternal serum sulphate levels are elevated in pregnancy because of the increase in activity of the sulphate transporter in the kidney and ileum (SLC3A1). In addition, a sulphate transporter in the placenta (SLC13A4) maintains the sulphate supply to the foetus[80] (Figure 4). Specific sulphotransferases transfer sulphate from 3′-phosphoadenosine 5′-phosphosulphates to multiple functionally essential molecules, including glucocorticoids, and the degree of sulphation may have important consequences in the immature foetus and infant (Figure 4). The enzyme involved in sulphation of AA increases after birth.[81] Enteral feeding and endogenous catabolism provide sulphate after birth. Most known genetic variants of AA metabolism affect glucuronidation.[82] Gilbert's syndrome, a multiplex genetic defect in glucuronidation,[83] causes hyperbilirubinaemia, and some of these mutations may also affect the conjugation of AA. Despite apparently low AA toxicity in very immature infants, pharmacovigilance and prospective follow-up is required.

Accidental AA overdose cases have been reported in neonates. In one report, a high-risk level (140 mg/L [0.94 mmol/L], 4 hours after the administration; reference range: 10–30 mg/L) was evident and infants were treated with N-acetyl cysteine (NAC). One 12-day-old infant, born at 25.5 weeks, accidentally received AA at 445 mg/kg AA (2.94 mmoles/kg) iv in a 1-hour period. A high AA serum level (180 mg/L, 1.2 mmol/L) was detected, and the apparent half-life of AA was 23.4 hours. The child was promptly treated with NAC, and no serious toxicity was detected.[84] Most reported AA overdose cases involve near term- or term-born infants. In two iatrogenic overdose cases reported, a transient, asymptomatic increase in prothrombin time was detected. One post-term infant had a high level of unconjugated bilirubin and transient signs of encephalopathy.[84] On the other hand, large quantities of NAPQUI, generated in the maternal liver, may enter the foetal compartment and cause foetal toxicity. NAC treatment of mothers is likely to benefit the foetus, too.[74]

According to pharmacodynamic evaluation, the AA-induced PDA contraction is dependent on the length of gestation and is less effective among infants born at 23–26 weeks' gestation (Treluyer JM et al., unpublished). In one study, an increase in dosage and duration of AA treatment increased PDA closure in infants and mice.[85] The planned TREOCAPA project includes a dose-response trial, involving stepwise increases in both the loading and maintenance doses (starting iv. 20 mg/kg and iv, and 7.5 mg/kg q4).[20] The most effective and safe dosage regimen will be chosen for infants born at 23–26 weeks and participating in the TREOCAPA phase III trial. Non-human studies have revealed a risk of oxidative stress with a high AA doses, and therefore, it not possible to exclude the likelihood that similar adverse effects will be evident in some sensitive infants.[86]

6.2 | Further augmentation of the efficacy and safety of AA-induced early PDA closure?

In immature infants, respiratory distress syndrome and a delay in PDA closure are closely associated.[13,36] They coincide with the oxidative challenge due to cytokines and free radicals.[87] Early PDA closure may facilitate early respiratory management; for instance, a surfactant therapy-induced increase in PDA shunt is avoided.[9]

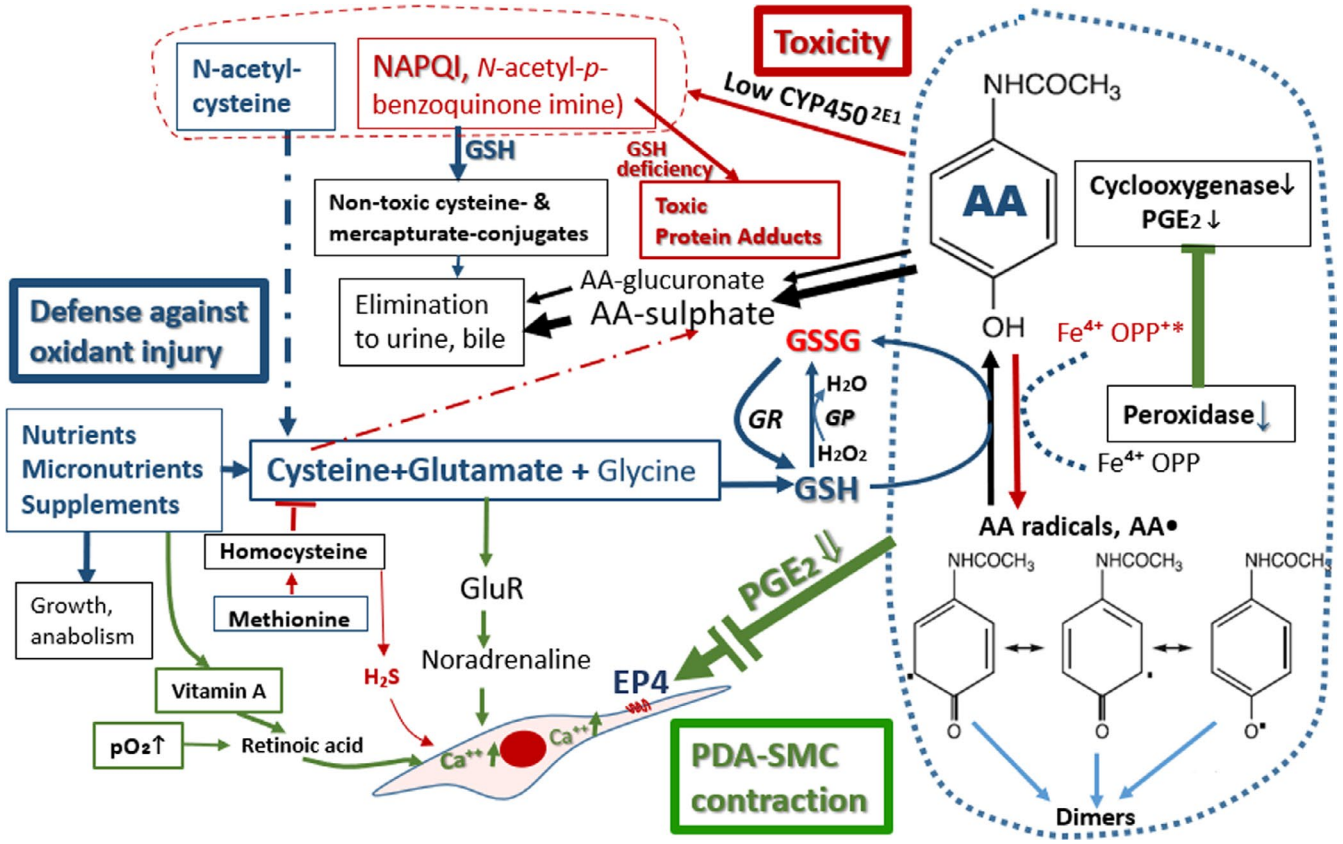

FIGURE 3 Linkage of the pharmacodynamics of acetaminophen (AA) and the glutathione (GSH) metabolism. Abbreviations: EP4, E-type prostanoid receptor 4; $^{Fe4+}$ OPP, ferryl protoporphyrin radical; GluR, glutamate receptor; GP, glutathione peroxidase; GR, glutathione reductase; SMC, smooth muscle cell. *Right*: Red-ox interaction of AA with peroxidase activity and GSH in regeneration of AA from oxidised AA•. *Below*: Pathways leading to contraction of PDA-SMCs. Deficient pathways (green) may be activated. *Centre*: Brief illustration of the synthesis of GSH. Deficiency of cysteine, glutamate and synthesis of glutamyl-cysteine are rate-limiting in GSH synthesis. Glutamate and vitamin A may activate PDA contraction. *Above (red)*: Low toxicity of AA in an immature newborn due to low CYP450 activity, resulting in synthesis of toxic NAPQUI. Administration of N-acetylcysteine (NAC) in AA toxicity provides cysteine for GSH. Low clearance rate of AA due to low conjugation rate almost exclusively to AA sulphate

Acetaminophen is a reactive molecule (Figure 2C).[71] Elimination of AA radicals and that of NAPQUI require glutathione (GSH) (Figure 3). Cysteine (Cys) and glutamic acid (Glu) are the critical precursors of GSH.[88,89] AA cysteine and AA mercapturate, non-toxic GSH reduction products of NAPQUI, were detected in VLGA infants after a single dose of AA (20 mg/kg iv), whereas NAPQUI remained undetectable.[77] This suggests that some NAPQUI is synthetised and de-toxified in immature infants. The liver of an immature foetus may not be capable of endogenous Cys synthesis and low Cys levels have been detected in umbilical blood at very preterm birth, suggesting a deficiency in maternal Cys supply.[90] Amino acid supplementation in preterm infants increased GSH in erythrocytes.[91] To our knowledge, Cys or NAC supplementation to the mother during imminent birth of an immature infant has not been studied. However, Cys or NAC may augment the GSH synthesis that is required during oxidative stress after birth and GSH may promote the AA-induced PDA closure (Figure 3).

The concentration of serum glutamate (Glu), an essential amino acid and precursor of GSH, decreases within two days after birth in VLGA infants.[60] According to experimental evidence, Glu enhances cardiac contractility and PDA contraction [60,92] (Table 2).

Corticosteroids accelerate pulmonary and cardiovascular development. In addition, they suppress inflammation and the formation of free radicals.[93] However, glucocorticoids dose-dependently decrease growth. In one study, low-dose hydrocortisone supplementation given immature infants eliminated endogenous cortisol deficiency, decreased the risk of PDA and increased survival without BPD.[94] However, NSAIDs, particularly in combination with corticosteroid, increased the risk of gastrointestinal bleeding and focal intestinal perforation. AA treatment with or without corticosteroid has not been associated with intestinal symptoms. AA may still influence the gut microbiota and cause dysbiosis or perforation in infants, unless proven otherwise.[74] Besides inhibition of PG synthesis, AA interacts with other pathways.[71,74] In the CNS, the effects of AA on pain and thermoregulation are associated with the inhibition of COX2 activity, and AA also stimulates the cannabinoid pathway and vanilloid receptors.[74]

Acetaminophen given to mothers in imminent VLGA birth did not constrict foetal PDA,[32] unlike NSAIDs.[29] Acetaminophen-induced

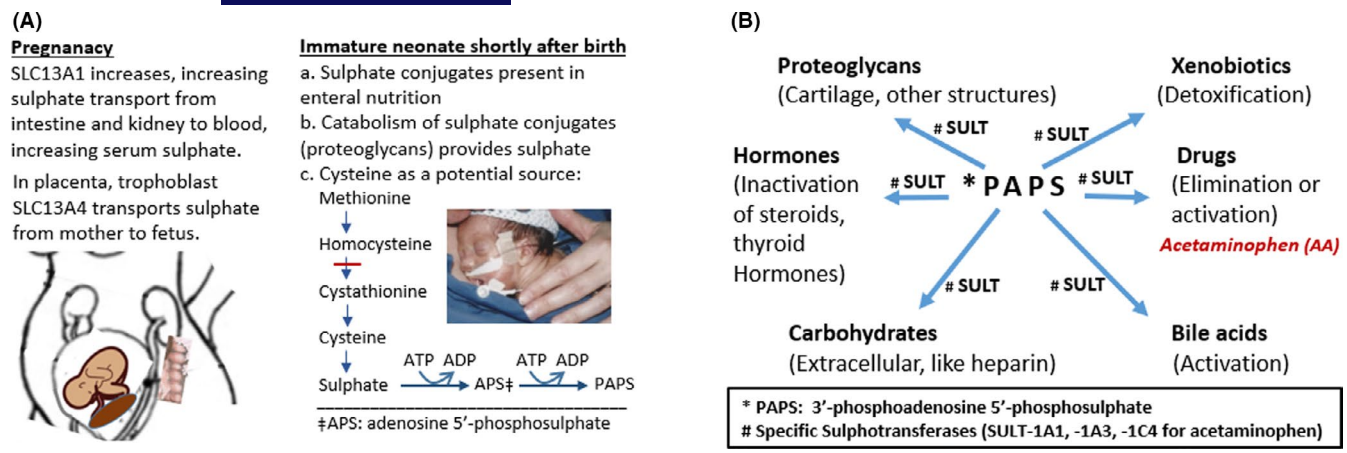

FIGURE 4 Sulphation pathways and sulphate supply to the foetus and neonate shortly after birth. (A) Sulphate supply to the foetus and the immature newborn. During first 1–2 days after birth of the immature infant, synthesis of cysteine is likely inadequate and it may be metabolised to sulphate. (B) Specific sulphotransferases catalyse sulphation of several compounds. SULT-1A1 predominantly catalyses the formation of AA sulphate. Sulphation may inactivate steroid and thyroid hormones in foetal compartments

PDA contraction soon after birth may depend on interaction with a critical level of O_2 tension.

7 | DISCUSSION

In many extremely premature infants, a left-to-right PDA shunt often starts early after birth and increases gradually, while in other immature infants the PDA closes spontaneously soon after birth. A PDA shunt perturbs both systemic and pulmonary flows[41] (Figure 1B), and it may increase the risk of cardiac dysfunction and chronic lung disease. An association between a large PDA shunt, systemic hypoperfusion and increased morbidity is evident and is biologically plausible.[3,95,96]

The effects of NSAIDs and AA are different. NSAIDs inhibit the synthesis of PGE_2, PGI_2 and TxA_2. All of them affect PDA during neonatal transition by different mechanisms (Table 2), and NSAIDs predispose individuals to bleeding, immune dysfunction and vasospasm. Acetaminophen preferentially inhibits PGE_2 synthesis.[71] A low AA dosage promoted PDA contraction without detectable adverse effects in immature infants.[27,28] Low CYP450^{2E1} activity limits the formation of toxic NAPQUI in preterm infants[97] (Figure 3), and occasional iatrogenic overdosage of AA has not caused serious adverse effects in preterm infants.[84] Furthermore, the effect of AA on PDA contraction may prove to be strongly dependent on oxygen saturation.[29,32]

Acetaminophen toxicity in children and adults is associated with a deficiency in GSH that eliminates the toxic oxidation product, NAPQUI (Figure 3). The immature liver has a low activity of enzymes catalysing the formation of NAPQUI, and this protects the neonate from AA toxicity.[76] However, the detoxification products of NAPQUI, AA cysteine and AA mercapturate, have been detected in neonates after moderate doses of AA.[78] Critical GSH deficiency is linked to inflammatory diseases, starvation and AA toxicity.[98] Cysteine and glutamate as precursors of GSH have important roles in the maintenance of a reduced intracellular environment.[88] The formation of glutamyl-cysteine is rate-limiting in GSH synthesis, and undetectable χ-glutamyl-cysteine synthase activity has been observed in the liver in connection with very premature birth.[89] As a result of a low or absent rate of synthesis of cysteine from methionine, cysteine is an essential amino acid in immature infants at birth[99] (Figure 3). A low level of GSH in cord blood has been associated with a low concentration of cysteine in high-risk mothers.[86] Also, the concentration of glutamate decreased within two days after extremely premature birth.[59] Glutamate may promote cardiac contractility, and in rats, glutamate increased PDA contraction.[59] Finally, retinoic acid enhances PDA contraction by enhancing the O_2 sensor effect on PDA in vitro (Table 2), and vitamin A supplementation in cases of imminent premature birth increased retinoic acid in cord blood.[100] However, parenteral vitamin A after birth has not decreased the risk of PDA. The onset of supplementation of critical micronutrients (cysteine, glutamine, retinoic acid) may already be required during imminent premature birth.

Ibuprofen, indomethacin and AA have been compared in randomised clinical trials[5,6,17-19] (Table 1). There are still open questions concerning the role of AA in the management of PDA.[101] Very soon after birth, the frequencies of both medically induced and spontaneous PDA closures are high. Most notably, the PDA closures are strikingly dependent on the duration of pregnancy.[2,19] A desirable drug for PDA closure would be effective and well-tolerated in extremely premature infants. Large trials on the efficacy of AA in the high-risk population are currently not available.[20] Although there were no detectable adverse effects in the trials carried out so far,[5,6,17] a modest and transient decrease in blood pressure following the loading dose of AA has been observed.[101] According to some reports, the use of AA in pregnancy was associated with the risk of asthma,[34] ADHD and autism[35] in later life. These results have not been confirmed in all studies, and the recall bias cannot be ruled out. However, the foetus may be susceptible to AA toxicity induced by NAPQUI from the mother. Therefore, the immature neonate

may prove to be better protected against AA toxicity than the foetus.[28,35,84,102] Further studies are required to confirm the beneficial and adverse effects of AA during early life.

8 | CONCLUSION

A targeted approach in the closure of haemodynamically significant PDA is currently recommended. In the present review, we consider the prophylactic management of PDA, using AA. Other drugs and managements, among others, supplementation with specific micronutrients and a low-dose steroid supplementation during perinatal transition may interactively strengthen the defence system and augment neonatal PDA closure during AA treatment. Achieving a seamless early PDA closure would help us to solve the old debate as to whether early PDA closure promotes intact survival of immature infants.

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CONFLICT OF INTEREST

No conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

MH planned the review, wrote the first draft and corrections, and planned tables and figures; JMT gave important idea and reviewed the manuscript; OA reviewed, inspired and helped to shape up the manuscript; and J-CR inspired, corrected and wrote additions to the manuscript.

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