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REVIEW

ATP-binding cassette (ABC) drug transporters in the developing blood–brain barrier: role in fetal brain protection

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Abstract

The blood–brain barrier (BBB) provides essential neuroprotection from environmental toxins and xenobiotics, through high expression of drug efflux transporters in endothelial cells of the cerebral capillaries. However, xenobiotic exposure, stress, and inflammatory stimuli have the potential to disrupt BBB permeability in fetal and post-natal life. Understanding the role and ability of the BBB in protecting the developing brain, particularly with respect to drug/toxin transport, is key to promoting long-term brain health. Drug transporters, particularly P-gp and BCRP are expressed in early gestation at the developing BBB and have a crucial role in developmental homeostasis and fetal brain protection. We have highlighted several factors that modulate drug transporters at the developing BBB, including synthetic glucocorticoid (sGC), cytokines, maternal infection, and growth factors. Some factors have the potential to increase expression and function of drug transporters and increase brain protection (e.g., sGC, transforming growth factor [TGF]-β). However, others inhibit drug transporters expression and function at the BBB, increasing brain exposure to xenobiotics (e.g., tumor necrosis factor [TNF], interleukin [IL]-6), negatively impacting brain development. This has implications for pregnant women and neonates, who represent a vulnerable population and may be exposed to drugs and environmental toxins, many of which are P-gp and BCRP substrates. Thus, alterations in regulated transport across the developing BBB may induce long-term changes in brain health and compromise pregnancy outcome. Furthermore, a large portion of neonatal adverse drug reactions are attributed to agents that target or access the nervous system, such as stimulants (e.g., caffeine), anesthetics (e.g., midazolam), analgesics (e.g., morphine) and antiretrovirals (e.g., Zidovudine); thus, understanding brain protection is key for the development of strategies to protect the fetal and neonatal brain.

Keywords Blood–brain barrier · ABC transporter · Fetal · Prenatal glucocorticoids · Maternal infection

Introduction

The blood–brain barrier (BBB) provides essential neuroprotection from environmental toxins and xenobiotics that may be circulating in the peripheral blood, through high expression of drug efflux transporters in endothelial cells of the cerebral capillaries. The BBB plays a key role in maintaining an optimal microenvironment for neuronal cells through hormone, nutrient and ion transport, as well as removal of waste products [1]. However, changes in its surrounding microenvironment, such as xenobiotic exposure, stress and inflammatory stimuli, have the potential to disrupt BBB permeability and induce brain injury, neurodegeneration and disease [2].

The developing fetal brain is highly susceptible to the influences of environmental factors; thus understanding the role and ability of the BBB in protecting the developing

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brain, particularly with respect to drug/toxin transport, is key to long-term brain health. In this regard, a number of drugs prescribed during pregnancy are actively transported at the level of the placenta and the fetal BBB. This review focuses on the ontogeny and regulation of key ATP-binding cassette (ABC) drug efflux transporter systems at the BBB, P-glycoprotein (P-gp; encoded by *ABCB1*) and breast cancer resistance protein (BCRP/*ABCG2*); which among other solute carrier (SLC) transporters, such as organic anion transporter 2 (OAT2/*SLC22A7*) and monocarboxylate transporter 1 (MCT1/*SLC16A1*), are present at high levels at the human BBB [3].

The role of the placenta in fetal brain protection, and how the fetal BBB and the placenta coordinate to protect the developing fetal brain will also be considered. Finally, we outline potential modulators of BBB-efflux transporter function during development, including exposure to infection, corticosteroids, and other modulators, which will directly impact fetal brain permeability and protection. Knowledge as to how brain protection is acquired and disrupted during development may offer new opportunities to reduce obstetric complications and improve pediatric outcomes.

BBB structure and function

The BBB is a highly organized biological system providing a physical barrier between the brain and the systemic circulation. Histologically, the BBB is comprised of brain microvessel endothelial cells (BEC)s, connected by intricate tight junctions, ensheathed at the abluminal surface by astrocyte foot processes and resident pericytes, which aid in the regulation of endothelial cell permeability (Fig. 1A). At the level of cerebral capillaries, this barrier is essential, as in the adult human, it covers a large surface area (12–18 m^2) with

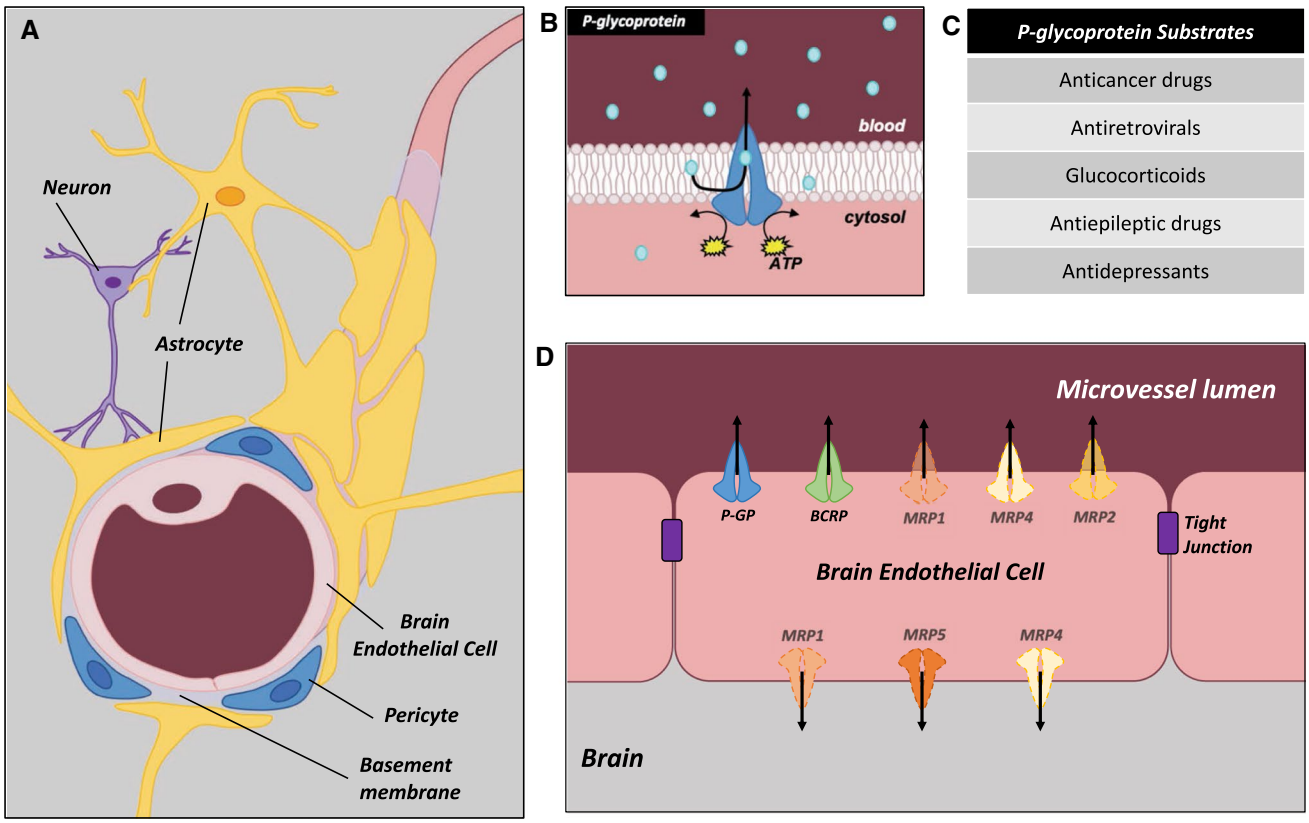


Fig. 1 Cellular structure of the blood–brain barrier (BBB). **A** Cerebral capillaries are ensheathed by astrocyte foot processes, and share a continuous basement membrane where pericytes are located. Nearby neurons make contact with astrocytes. Together these cells form the BBB or "neurovascular unit". **B** Mechanism of substrate efflux. P-glycoprotein (P-gp) is a transmembrane transporter that effluxes its substrates against their concentration gradients by utilizing ATP. Studies have shown that P-gp acts as a flippase, grabbing lipophilic substrates as they cross the plasma membrane, and excluding them. **C** Categories of P-gp substrates. Listed are some of the major categories of P-gp substrates. Most P-gp substrates are lipophilic and there is large substrate overlap with other drug transporters. **D** Localization of drug transporters in brain endothelial cells. P-gp and breast cancer resistance (BCRP) protein are primarily localized at the luminal side of BECs where they prevent entry of their substrates into the brain parenchyma. Multidrug-related proteins (Mrp) 1,3, 4, 5 have been detected in brain endothelial cells, and some studies have suggested their localization to the luminal or basolateral side of endothelial cells

a diffusion distance of 25 μm between the lumen and nearby neurons (to maximize cerebral–blood exchange rates) [4]. Here, we summarize important features of the BBB components related to brain protection.

Endothelial cells

At the BBB, endothelial cells have several unique characteristics compared to those in the systemic circulation. These include low vesicular transport, and high expression of nutrient and drug transporters, with the latter controlling transcellular passage of molecules into and from the brain. One study found BECs also have a higher mitochondrial volume compared to systemic endothelial cells [5], which many postulate supports diverse specialized active transport systems [1, 6]; however, more research is required to confirm this relationship.

Cerebral capillaries lack fenestrations and possess unique tight junction structures to efficiently restrict paracellular transport [7]. The high complexity and number of tight junctions are unique adaptive features of BECs compared to other endothelial cells [8, 9]. The primary proteins that make up tight junctions in BECs are occludins, claudins, and zonula occludens. Occludin, a 65kDA protein, with 4 transmembrane domains was the first integral membrane protein discovered at the tight junction. However, knockout of occludin did not affect tight junction strand formation, suggesting the necessity of other membrane proteins at the tight junction [10]. The claudin family of proteins has a similar structure to occludin but shares little sequence homology. In the brain, claudins-5 is specifically expressed in endothelial cells and not at tight junctions of other cell types [11]. Knock-out of *Cldn5* in mice leads to size-selective leakiness at the BBB, and was therefore deemed the integral protein of the tight junction system [12]. Zonula Occludens (ZO) proteins connect the intercellular domains of the tight junction to the cytoskeleton and add structural support [4]. Together, tight junction proteins confer an important barrier by restricting the intercellular space and therefore limiting the entrance of molecules as small as 4.7 ˜A (sucrose) [13]. Additionally, the combination of a small intercellular space and charged extracellular loops of claudin proteins, results in limited paracellular ion transport. The restricted movement of charged molecules across the paracellular space creates high resistance across the cerebral endothelium and helps to establish concentration gradients [7, 8, 14]. However, many potentially toxic endogenous and exogenous compounds are lipophilic, and able to freely cross transcellularly via passive diffusion across the plasma membrane. In this case, protection is provided by active transporter systems in the BBB (discussed in detail in "ATP-Binding Cassette (ABC) Transporters"), which limit the entry of a myriad of lipophilic and non-lipophilic drugs and environmental toxins into brain [15].

Pericytes

Pericytes play a key role in maintaining BBB homeostasis and integrity through secreted factors and regulation of tight junction integrity and vesicular trafficking. Pericyte coverage is higher in brain vessels than in any other tissue vasculature. Pericytes together with astrocyte foot processes are present in the basement membrane of capillary endothelial cells (Fig. 1A), and make direct contact with endothelial cells via adheren (N-cadherin) and gap junctions (connexin 43) [16]. During BBB development in mice, pericytes are closely associated with BECs, and are present from initial migration of the vascular plexus into the neural tissue [17]. Pericytes are key cellular components modulating specificity of transport across the neurovascular unit since they reduce vesicular trafficking in endothelial cells [18]. In mice, decreased pericyte number is associated with increased BBB permeability resulting from structural abnormalities in endothelial cell contacts, despite normal tight junction formation [17, 19]. Regulation of BECs by pericytes appears region-specific since a uniform reduction in pericyte number throughout the brain only affects BBB permeability in some specific regions (e.g., cortex, hippocampus) [20]. Less is known about the role of pericytes in specifically regulating drug transporter expression at the BBB. One study identified increased P-gp function in mouse immortalized brain capillary endothelial cells after co-culture with rat brain pericytes; this effect was in part mediated by transforming growth factor beta (TGF-β) secreted by pericytes [21]. The specific intracellular signaling pathways involved in TGF-β mediated upregulation of P-gp and BCRP at the BBB are unknown. Recently, studies in hepatocellular carcinoma cells have implicated miRNAs and lnRNAs in mediating the effects of TGF-β induction of P-gp and BCRP expression. Specifically, a SMAD4/HOTAIR/miR-145 axis was identified that responds to TGF-β by up regulating P-gp and BCRP [22]. While, this signaling pathway has not been investigated in physiological/non-cancerous tissues, it could be hypothesized as one possible mechanism mediating pericyte regulation of P-gp and BCRP expression/function in BECs. Of note, TGF-β is also secreted by astrocytes, and plays a key role in maintaining BBB integrity via regulation of P-gp. However, another study found no change in *Abcb1* mRNA expression after co-culture with pericytes [23]. The mechanisms through which pericytes regulate drug transporters in BECs warrants further investigation.

Astrocytes

Astrocyte foot processes surround the abluminal face of endothelial cells, and share a continuous basement membrane (Fig. 1A) [24]. Astrocytes regulate tight junction function between endothelial cells, decreasing the size of the intercellular cleft [25]. This has been demonstrated in in vitro co-cultures of astrocytes and BECs, where transendothelial electrical resistance (TEER), is increased [26, 27]. By inducing tight junction function, astrocytes also contribute to the polarization of transporters to the luminal membrane, including the GLUT1 glucose transporter and P-gp. Astrocyte-endothelial cell interactions lead to differentiation in both cell types. Agrin in the basal lamina, which is a heparin sulfate proteoglycan, secreted by endothelial cells at the time of BBB tightening, stimulates polarization of astrocytes, including sequestering of the water channel aquaporin 4 (AQP4) to astrocytic end feet [28]. In this connection, in a rat model of temporal lobe epilepsy, disruption of aquaporins expression by the drug acetazolamide, leads to disruption of P-gp expression in hippocampal tissue [29]. Furthermore, astrocyte secreted factors also increase expression and function of the efflux drug transporter P-gp in BECs from neonatal guinea pigs [27], further demonstrating an interplay between these two cell types regulating transport function at the developing BBB.

ATP-binding cassette (ABC) transporters

The ABC transporters are critical for maintaining brain homeostasis and provide a route for xenobiotic clearance from the cerebral parenchyma into the circulation. The human ABC superfamily of efflux transporters consists of 48 proteins, divided into seven subfamilies from *ABCA* to *ABCG* [30]. In humans and mammals, the ABC superfamily is largely comprised of drug and lipid transporters, and generally possess a basic structure with four domains. Two transmembrane domains (TMD) hold the transporters in the lipid bilayers and are responsible for substrates' permeation, and two nucleotide-binding domains (NBD), responsible for ATP-driven energy supply [31].

The ABC drug transporters P-gp (encoded by *ABCB1* in humans and by *Abcb1a* and *Abcb1b* in mice and rats), BCRP (encoded by *ABCG2*), and the Multidrug Resistance Proteins, isoforms 4 and 5 (Mrp 4 and 5, encoded by *ABCC4* and *5,* respectively) are the most abundant ABC drug transporters at the BBB. Prior to determining their role in physiological barrier sites (i.e., placenta, kidney, intestine, BBB) P-gp and BCRP were first identified and studied as sources of multidrug resistance (MDR) in cancer cells [32, 33]. P-gp and BCRP are highly expressed in the luminal surface of the BECs (facing the systemic circulation) [3, 34, 35], although some studies have shown that they may also be weakly localized on the abluminal membrane (facing neuronal tissue) [36] (Fig. 1). Drug transporters have a wide spectrum of substrate specificities, with some overlapping substrates. Pharmaceutical agents that are substrates for ABC transporters include anti-cancer drugs, HIV inhibitors, opioids, antibiotics, antidepressants, antiepileptics, immunosuppressants and synthetic glucocorticoids (sGC) among others [37, 38]. Table 1 presents a summary of important ABC transporter substrates. Drug transporters exert an essential function in reducing the transfer of pesticides, toxins, and potentially harmful substances from the systemic circulation into the brain. However, they also represent a challenge to therapeutic treatment of brain tumors as they limit drug bioavailability, a major obstacle, for example, in the use of peripherally administered anti-cancer drugs. Additionally, drug transporters regulate the uptake of several endogenous substrates (e.g., steroids, lipids) that may be important for normal function and development.

P-gp is one of the major BBB drug transporters and is the most well-studied ABC transporter, based on its crucial role in neuroprotection and drug resistance. P-gp, is predominantly located on the luminal surface of BECs [50–52] (Fig. 1), where it functions as a drug transporter at the plasma membrane excluding a large spectrum of substrates (please see Table 1). P-gp is also localized intracellularly in the Golgi complex, endosomes/lysosomes/proteasome and in the endoplasmic reticulum (ER) which are important sites for P-gp post-translational modification, traffic/recycling/degradation and synthesis, respectively [53–56]. P-gp has a predicted molecular weight of 140 kDa, and the mature N-glycosylated protein migrates through SDS-PAGE at an apparent molecular weight of 170 kDa [57, 58]. P-gp protein and *Abcb1* mRNA have also been identified in the primate brain parenchyma, neuronal and glial cells, though at lower levels than in the BEC [59–61]. In this context, while the expression of P-gp and BCRP is likely of importance, less is known about their functional role in neuronal and glial cells.

Functional P-gp deficiency dramatically increases transfer of many drugs and xenobiotics into the brain. In vivo studies in *Abcb1* knockout mice revealed up to 100-fold increased brain accumulation of P-gp substrates [50, 62, 63]. Further, exposure to ivermectin during pregnancy in mice, lead to congenital head anomalies in 100% of homozygous $Abcb1^{-/-}$ offspring [64]. Recently, an epidemiological study supported the effect of P-gp in protecting the fetal human brain, by showing an increased risk for specific CNS congenital anomalies after exposure to clinical P-gp substrates (including cimetidine, ranitidine, risperidone, citalopram) along with the use of P-gp inhibitors (including omeprazole, pantoprazole, haloperidol) in women in the first-trimester of pregnancy [65].

Table 1 Blood–brain barrier ABC transporters and their major substrates relevant in pregnancy and neonatal life

Class	Substrate	ABC transporter(s)	Relevance in pregnancy and neonatal life	References
Anti-epileptic	Phenobarbital	P-gp	First-line treatment for most neonatal seizures	[39, 40]
	Lamotrigine	P-gp	Safe for use during pregnancy (26,416,395)	[39, 41]
	Phenytoin	P-gp Mrp1	Second line treatment for neonatal seizures	[39, 40, 42]
	Topiramate	P-gp	Second-generation AED, sometimes used to treat refractory neonatal seizures (Sandoval 2019)	[39, 40]
Anti-HIV	Zidovudine	P-gp BCRP Mrp4	Indicated for treatment of neonates with HIV	[43, 44]
	Ritonavir	P-gp Mrp1, Mrp2	Infants and children, combined with Lopinavir	[42, 45]
	AZT	BCRP Mrp4	Safe for use in pregnant women and their infants in combination w/Zidovudine	[42, 46]
Analgesics	Morphine	P-gp	Management for post-operative pain	[39, 47]
	Methadone	P-gp	Neonatal abstinence syndrome; therapeutic treatment for opiate abuse during pregnancy	[47, 48]
Anti-cancer	Doxorubicine	P-gp BCRP Mrp1, Mrp2, Mrp6		[42]
	Mitoxantrone	P-gp BCRP		[42]
	Daunorubicin	P-gp BCRP Mrp1, Mrp6		[42]
	Methotrexate	P-gp Mrp1, Mrp2, Mrp3, Mrp4		[42]
Anti-depresssants	Amitryptiline	P-gp	Increased rate of cardiac abnormalities when taken during pregnancy	[42, 49]
	Doxepin	P-gp	No increased incidence of neonatal cardiac abnormalities when used during pregnancy	[42, 49]
Other substrates	Verapamil	P-gp Mrp1	Calcium channel blocker; a competitive inhibitor of P-gp	[42]
	Cyclosporin A	P-gp Mrp1	Immunosuppressants; also a competitive inhibitor of P-gp	[42]

Although P-gp was the first drug transporter described at the BBB [66, 67], BCRP is the most abundant ABC transporter in the human BBB at the level of protein [68] and mRNA [69]. BCRP is a "half-transporter", with 70 kDa and only one TMD and one NBD, that requires homodimerization to become functionally active [70]. Similar to P-gp, BCRP is highly expressed in the luminal membrane of brain microvascular endothelium (Fig. 1) [71]. The absence of BCRP in *Abcg2*$^{-/-}$ mice results in increased accumulation of BCRP substrates in the brain [72, 73]. Intracellular localization of BCRP has also been demonstrated in many cell lines [74–76]; however, specific localization and function in organelles/vesicles in developing BBB require further investigation.

P-gp and BCRP have overlapping substrates, and a number of studies have suggested a synergistic/complimentary relationship between the two transporters [77–88]. There is evidence for a compensatory mechanism by which downregulation of one transporter results in increased expression and function of the other [89–91]. In coordinating the response to infection, this appears to be the case. In hCMEC/D3 cells, LPS and poly:ic exposure results in increased P-gp function but decreased BCRP activity. ssRNA-40 had the opposite effect where P-gp function was decreased, but BCRP activity increased [92]. This complementary relationship may be due to differences in the signaling pathways induced by different infective insults. Cross-talk between the regulatory pathways of P-gp and BCRP likely has important implications for drug delivery into the brain. While there is a considerable knowledge of P-gp regulation at the BBB relatively little is known concerning the mechanisms regulating BCRP expression and function. Further studies are required to better understand the potential cross-talk between these two transporter systems in the developing brain.

MRPs are a subfamily of ABC transporters with 13 members, that are generally larger than other ABC transporters; approximately 200 kDa [93]. MRP-1 to 6, 9 and 10 have been detected in human BECs, with MRP4 and 5 expressed at highest levels [34, 35, 94, 95]. MRPs are present either at the luminal or abluminal membranes or both in BECs, and contribute to efflux of substrates in both directions at the BBB [36, 96–99]. MRP substrates include antibiotics, antiretrovirals, immunosuppressive drugs, antiepileptic and anti-cancer agents [100–102] (Table 1). However, relatively little is known concerning the regulation of MRPs or the expression and regulation of other ABC transporters in the adult or developing BBB; many of which may have important transport functions.

Other ABC transporters have been detected at the rodent and human BBB, through mass spectrometry-based proteomics. These include the ABCA superfamily, which are involved in lipid transport (e.g., cholesterol) [3]. ABCA2 and ABCA8 are the two most abundant ABC transporters at the BBB after BCRP and P-gp. However, their functional role remains unclear. ABCA2 is expressed in several brain cell types including oligodendrocytes, some neurons, and brain endothelial cells. Studies in oligodendrocytes have determined that ABCA2 is localized to the lysosomal compartment, rather than the plasma membrane, and could therefore be involved in intracellular lipid transport [103, 104]. Importantly, there is increasing recognition for the role of specific ABC transporters proteins, such as ABCA1, ABCA2, BCRP, MRP-1 and P-gp clearing β-amyloid protein (the major amyloid plaque component) out of the brain. As such, dysregulation of ABC transporters has therefore been implicated in the pathogenesis of Alzheimer's Disease [105, 106]. Since ABCA1 has been demonstrated to neutralize β-amyloid aggregation capacity via Apolipoprotein E (ApoE) [107], the expression of ABCA1 and ABCA2 at the BBB as a site of waste removal from the brain, may suggest a potential role in Alzheimer's disease, which warrants further investigation. Little is known about the ontogeny of ABCA transporters or a potential role at the BBB during development. As Kim et al. postulated in their 2008 review, ABC transporters involved in lipid transport, that are expressed in the brain, likely play an important role in brain–lipid homeostasis.

In addition to the BBB, which is the focus of this review, ABC and other drug transporters are expressed elsewhere in the central nervous system (CNS), including the blood–cerebral spinal fluid barrier (choroid plexus), blood–retinal barrier and spinal chord. In this context, P-gp has been described in the epithelial cells of the (choroid plexus) of mouse, rat and human, where it may act in the regulation of the efflux transport function in the cerebrospinal fluid (CSF) [99]. In the porcine blood–retinal barrier, BCRP, P-gp and MCT1 transporters were detected, demonstrating a potential role of these transporters in regulating xenobiotic clearance in different types of CNS-related barriers. A detailed review of other brain barriers during development can be found here [108].

BBB development

The onset of the brain vasculogenesis is well documented in mice. It begins at gestational day (GD) 7.5 with the migration of mesenchyme-derived angioblasts into the outer part of the neural tube head region to form a perineural vascular plexus (PNVP) that sprouts and invades the surrounding inner neural tube, at around GD9.5 [109]. The newly formed vessels then lose their fenestrations, form tight junctions, and adopt a BBB phenotype [9, 110]. BEC tight junction complexes are observable as early as GD13.5 in mice, and 8 weeks gestation in humans [111]. While the process of brain vascularization, tight junction formation, and the factors that guide these events have been described [112], little is known about how and when drug transporter expression is induced and then regulated during development. This knowledge is key to our understanding of how maternal and external factors, isolated or combined, may affect BBB drug transporters during neurodevelopment, and in turn, uptake of substrates (i.e., toxins, xenobiotics, hormones) into the fetal brain.

During fetal brain development, the specialized phenotype of BECs is driven by factors secreted by pericytes and neural progenitor cells. Canonical Wnt-signaling is involved in driving vascularization of the developing BBB, by guiding angiogenesis in concert with vascular endothelial growth factor (VEGF) [112, 113]. Wnt is also involved in the induction of P-gp gene expression in the BBB. Differentiation of stem cells into BECs in vitro has also helped elucidate key factors in driving the maturation of the BBB. Sequential Wnt and retinoic acid (RA) pathway activation in human pluripotent stem cells (hPSCs) lead to their differentiation [114]. Direct and indirect effects of Wnt/β-catenin on P-gp expression have been demonstrated in models of adult and fetal BBB, where activation with Wnt ligands leads to increased P-gp expression and activity [115, 116]. Wnt/β-catenin signaling interacts with other pathways (e.g., TGF-β, Notch) that are activated by pericytes and neural progenitors during early vascularization [113]. TGF-β is secreted from pericytes and binds to the TGF-βII and I receptors on the abluminal face of endothelial cells to increase P-gp expression and activity. This has been demonstrated in vitro, in developing guinea pig BECs and in adult rat and murine endothelial cells [21, 117, 118]. TGF-β can also induce developing BBB tight junction function and be secreted by astrocytes [118]. In this context, we have shown that astrocytes in co-culture with BECs derived from the fetal and neonatal brain increase TEER, and reduce dextran movement across the monolayer [27]. Pericytes and not astrocytes

are present at the neurovascular unit from early BBB formation, and as such, secreted factors from pericytes are likely most important in initial BBB phenotype acquisition. The fact that P-gp and BCRP are regulated by key signaling pathways in embryonic and fetal development highlights their functional importance in the establishment and maturation of the developing BBB.

The ontogeny of drug transporters at the developing BBB is summarized in Table 2. Appearance of drug transporters is sequential, and different ABC transporters exhibit different developmental patterns of expression across gestation. P-gp is considered one the earliest markers of brain microvasculature, detectable at GD10.5 in mice, and has been detected as early as 6–8 weeks post conception in humans [111, 119, 120]. In humans, guinea pigs, mice and rats, levels of *ABCB1 (Abcb1)* mRNA and P-gp protein increase with development [96, 116, 121] (Fig. 2). Studies in mice and rats have also shown these increases in gene and protein expression correspond with increased P-gp function [122–124]. While limited studies have been undertaken, P-gp levels have been shown to be low in microvessels in early human BBB development, and primarily cytosolic. Toward 18 weeks of gestation, P-gp expression becomes diffuse along the length of capillaries, and by 22 weeks, P-gp is expressed evenly along cerebral capillaries [125]. See Table 2 and Fig. 2 for a summary of timing and pattern of P-gp expression at the developing BBB.

BCRP has been identified as one of the first ABC transporters expressed in the neurovasculature. Studies in humans and guinea pigs have identified expression of BCRP in cerebral capillaries from mid-gestation (22 weeks in human; GD 40 in guinea pigs), with little change in expression levels through fetal development [96, 129, 130]. However, studies in rats have reported increasing expression of *Abcg2*/BCRP during fetal BBB maturation, corresponding with an increase in BCRP activity [116, 123, 131], suggesting potential species differences in BCRP expression during BBB development. Recently, BCRP has been detected as early as 5 weeks post conception in humans, in the early stages of brain vascularization, before even P-gp is detectable by immunostaining [119]. BCRP is present in microvessels throughout gestation [96]; and of note, we have shown microvessels in 2nd trimester (~ 17 weeks) fetal brains to express both P-gp and BCRP (Fig. 2).

Table 2 Expression of ABC transporters at the developing BBB of human, guinea pig, mouse and rat

ABC transporter	Earliest expression at BBB during development			
	Human	Guinea pig	Mouse	Rat
ABCB1 (P-gp)	GW 7–8 [119, 120]	GD 40* [126]	GD10.5 [127]	GD13* [122]
ABCG2 (BCRP)	GW 5 GW [119]	GD 40* [126]	GD12.5* [128]	GD13* [122]
ABCC1 (MRP-1)	GW 5 GW [119]	N/A	N/A	GD13* [122]
ABCC4 (MRP4)	N/A	N/A	N/A	GD13* [122]

GW gestation week, *GD* gestation day, *N/A* not available

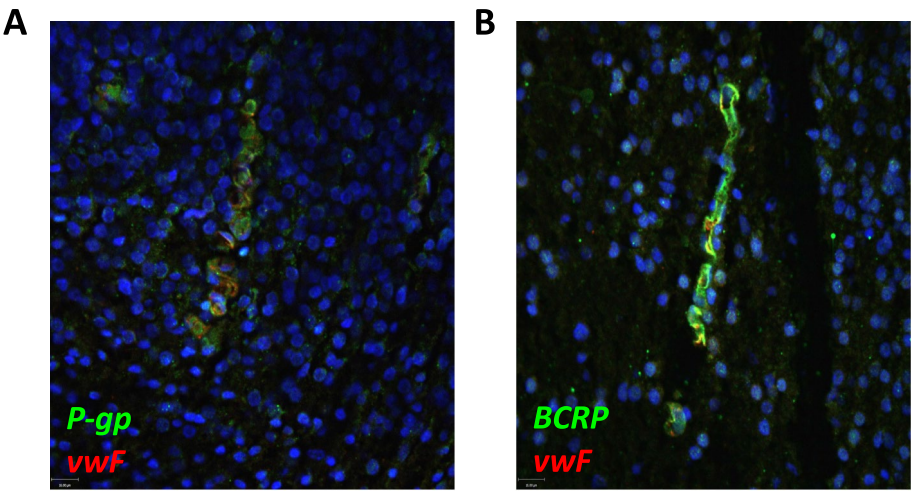
*Earliest studied

The role for P-gp and BCRP may not be limited to BBB protection during fetal brain development but may comprise other functions including modulation of migration of BBB cell precursors and angiogenesis, whereas in neural progenitor cells (NPCs) they may function as markers of immaturity/stemness. In this regard, our group has recently demonstrated that silencing of *ABCB1* (encoding P-gp) in human extravillous trophoblast cells (EVT; HTR8/SVneo) impaired invasion and migration and induced tube formation [132]. Similarly, silencing of *ABCG2* (encoding BCRP) inhibited EVT cell migration while it did not affect cell proliferation [133]. EVTs are endovascular invading cells with relatively high expression of P-gp and BCRP in capillaries early on in development. It is possible that P-gp and BCRP being present in BECs during phases of intense angiogenesis and lateral branching formation, may play a role in these processes; a hypothesis currently being investigated. With respect to NPCs, expression of *ABCB1* is high in early development when these cells are immature (Nestin positive) [134]. Upon differentiation, *ABCB1* expression is reduced, suggesting that beyond protecting an important stem cell pool, P-gp may have a role in stemness itself in this cell type. Taken together, the high expression of P-gp and BCRP in proliferative and invasive cell types, including side population cells and cancer cells, should be considered in discussing alternate roles for these transporters in the BBB.

MRPs are detectable in the fetal brain, however at lower levels compared to P-gp and BCRP. MRPs are present at higher levels in ependymal cells of the choroid plexus in humans and rats, compared to BECs [96, 98]. In humans, MRP-1 is present at high levels in the choroid plexus and cerebellum by 22 weeks gestation, but was undetectable in cerebral capillaries, suggesting a less important role for MRPs at the developing BBB [96]. However, another study detected Mrp1 in the human cerebrovasculature at 5 weeks post conception [119]. Further studies are required to elucidate the presence and role of MRPs at the developing BBB. Figure 2C provides a summary of developmental changes in drug transporter expression for the different species that have been studied, to date.

Drugs, environmental factors, and the developing BBB

Drugs are frequently used during pregnancy, particularly in cases of chronic diseases (depression, diabetes, epilepsy),



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	P-gp	BCRP	MRP1
Human	↑	↔	↔
Guinea Pig	↑	↔*	-
Mouse	↑	↔ / ↑	-
Rat	↑	↔ / ↑	↔

References for human [96, 119-121], guinea pig [126], mouse [124, 125, 129], rat [122, 123]
* Unpublished observation

Fig. 2 Developmental expression of drug transporters at the blood–brain barrier. P-glycoprotein (P-gp) **(A)** and breast cancer resistance protein (BCRP) **(B)** are expressed in second trimester human cerebral microvessels. Pattern of drug transporter expression throughout development in different species **(C)**. P-gp expression increases with advancing gestation in all species, while BCRP expression stays fairly constant. Little is known concerning the developmental regulation of multidrug resistance proteins (MRPs)

as well as to treat pregnancy-associated symptoms or infections [135]. Approximately 70% of women take at least one medication (excluding vitamins & supplements) during pregnancy [136, 137]. Many drugs prescribed during pregnancy are P-gp, BCRP and MRP substrates or modulate their activity. Given that increased drug exposure can negatively impact fetal brain development, it is critical to understand the levels and regulation of drug transporters in the developing BBB. Table 1 summarizes major classes of P-gp and BCRP substrates, with a focus on those relevant in pregnancy and neonatal life.

During pregnancy, the fetus and the developing brain may be exposed to factors present in the maternal environment. These include agrochemicals, toxins or their residues, that may enter the mother through water [138, 139], dietary [140, 141] or airborne routes [142, 143]. Exposure of the fetus to a number of these factors have been associated with altered pregnancy outcomes including preterm birth [144, 145] and reduced birthweight. Longer-term effects associated with prenatal and post-natal pesticide exposure have also been identified, such as increased blood pressure [146], altered glucose metabolism [147], poor respiratory outcomes [148, 149], and neurobehavioural deficits in children [150, 151]. For example, one study in this systematic review [150] found cord blood levels of chlorpyrifos were associated with attention deficits in toddlers; chlorpyrifos is known to interact with BCRP [152] and P-gp. Chlorpyrifos has been shown to regulate human BCRP expression in placental trophoblast cell lines [152] and placental explants [153, 154]. In addition to chlorpyrifos, several organochlorine and pyrethroid pesticides have been shown to regulate the expression and function of human P-gp and BCRP in vitro [155, 156]. Most studies investigating the effects of organochlorine and pyrethroid pesticides on human drug transporters must make use of in vitro cell culture or membrane vesicle preparations; studies identifying pesticides as P-gp or BCRP substrates face similar challenges. While knowledge of the in vivo role for drug transporter efflux of pesticides is limited, studies utilizing mosquitos have identified permethrin and temefos as potential drug transporter substrates [157, 158]. Epidemiological data on the effects of pesticides on human drug transporters in vivo, in particular at the BBB, are limited. Therefore, the possibility that drug transporters may play a crucial role in protecting the developing fetus from maternal pesticide exposure and subsequent short-term and long-term effects is an assumption that requires investigation. In this case, alterations in drug transporter function due to the presence of pharmacological or physiological (e.g., inflammation, infection) inhibitors, could increase accumulation of their substrates into the CNS. The impacts of infection

and pro-inflammatory cytokines on BBB drug transporter function are discussed in detail below. Increasing access of such pesticides and toxins to the fetus is likely to have consequences for development. A retrospective study found that when pregnant women were exposed in their first-trimester to both clinical P-gp substrates (including cimetidine, ranitidine, risperidone, citalopram) concurrently with P-gp inhibitors (including omeprazole, pantoprazole, haloperidol), this was associated with increased risk for specific congenital anomalies of the CNS [65]. Ultimately, more research is required to fully understand the role of fetal and placental drug transporters in preventing teratogenesis.

Cross-talk between the placenta and fetal BBB in protection of the developing brain

The human fetal brain is protected from xenobiotics by two key barriers: the placenta and the fetal BBB. The placenta represents the primary protective barrier separating maternal and fetal circulations, and it is important to note that the a greater proportion of the placenta is of fetal origin. The placenta delivers nutrients and oxygen to the fetus, while simultaneously functioning as a route for fetal metabolic waste elimination. In parallel, it limits the entrance of several factors present in the maternal circulation that could be harmful to the developing fetus. The placental barrier in humans is formed by syncytiotriophoblasts, which are in close contact with the maternal blood bathing the intervillous space [159]. A number of members of the ABC transporter family have been identified in the placenta, including P-gp, BCRP, MDR3 (encoded by *Abcb4*), MRPs 1,2,3,5 and the lipid transporters ABCA1, ABCA6 and ABCG1 [37, 160, 161]. Transport proteins may be present in the apical and/or the basolateral surfaces of the syncytiotrophoblast layer, facing both the maternal blood and the placental core in a transporter specific manner. This allows them to control the entrance and accumulation of substrates, depending on their placental location. A number of transporters are also be expressed in the luminal membrane of the fetal capillaries, controlling the efflux of substrates into/or out from the fetal circulation.

There is a critical interplay of the placenta and fetal BBB in protecting the developing fetal brain. Placental protection through the expression of efflux drug transporters is critical in early stages of pregnancy when fetal brain capillaries and the BBB are still being formed. The primary drug transporters, P-gp and BCRP are expressed at high levels in the placental syncitiotrophoblast in the first trimester human placenta [162–164]. P-gp and BCRP are expressed at the apical membrane, and efflux their substrates from the placenta to the maternal circulation [165]. Levels of placental P-gp decline in late gestation, while BCRP levels remain relatively constant [162–164]. Similar patterns have been identified in animal models [166]. In the mouse, the reduction in placental P-gp results in increased accumulation of P-gp substrates in the fetus and amniotic fluid [167]. In parallel to the decrease in protection provided by the placenta, there are increases in P-gp and BCRP in the fetal BBB [121, 124]. As such, it appears that the fetal BBB becomes critically important for brain protection in late gestation. This increase in protection also represents an important transition from fetal to post-natal life. In this context, in most mammalian species there is a major surge of endogenous glucocorticoid that occurs in late gestation, and emerging evidence would suggest this may drive the transition (discussed in detail below). The rising glucocorticoid levels correspond with up-regulation of P-gp, which also suggests developmental regulation of P-gp and BCRP is coordinated at least in part through separate signaling pathways (as BCRP does not increase). Additionally, emphasis has been placed on understanding the role of P-gp and BCRP in drug resistance/barrier function, when these transporters may have other physiological functions. The BBB also plays an important role in sequestering neurotransmitters such as serotonin, which cannot cross the BBB and thus must be synthesized locally in the CNS [25, 168]. This is important for neurotransmitter balance and signal specificity. It is likely that drug transporters play a role in controlling movement of key hormones/signals during development, an important area of research that requires further focus."

Glucocorticoids and the developing BBB

Glucocorticoids are key in the transition from fetal to neonatal life. The late gestation surge in fetal glucocorticoid is essential for maturing several organs, including the lungs, liver, kidney and brain. Glucocorticoids exert their actions via glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) signaling. As discussed above (see cross-talk), P-gp expression and activity at the BBB increases with advancing gestation. This maturation could be mediated by glucocorticoids, as both endogenous (cortisol), and sGC (betamethasone, dexamethasone) are potent modulators of drug transporter expression and activity, as well as tight junction function in the BBB [126, 129, 130, 169–171]. In the context of preterm birth (~ 12% of all pregnancies), antenatal sGC are administered to mature the fetal lung and reduce the risk of respiratory distress syndrome [172, 173] Unlike endogenous cortisol which binds both MR and GR, sGC are not inactivated by placental 11 beta HSD-2 and activate only GR [174]. We have shown in the guinea pig that maternal treatment of cortisol and sGC increase expression and function of BBB P-gp/*Abcb1* in late gestation/early postnatal life, but not in mid-gestation [126]. The role for glucocorticoids in inducing BCRP at the developing BBB is less clear. Administration of sGCs to pregnant mice led to altered

mRNA levels of *Abcg2* at the fetal BBB but not BCRP protein expression and function [124, 129], demonstrating a disconnect between mRNA and protein levels for this transporter. sGC increase trans-endothelial electrical resistance (TEER) in brain endothelial cells in vitro, and this is associated with increased tight junction function [175, 176]. In development, maternal antenatal dexamethasone exposure increases expression of tight junction proteins in the BBB of fetal sheep, and this was associated with decreased BBB permeability (increased function) [170, 171], thus showing strong evidence for modulation of fetal BBB transporter activity and permeability by sGC.

In addition to GR signaling, sGC also activate drug-sensing pathways via pregnane-x-receptor (PXR) and constitutive androstane receptor (CAR) [177–179]. PXR and CAR are nuclear receptors, which upon binding xenobiotics, translocate to the nucleus and activate transcription through binding "xenobiotic response elements" in genes, namely cytochrome p450 enzymes, and drug transporters in liver [180]. PXR and CAR are also expressed in brain endothelial cells [181]; it is likely that PXR and CAR play a role in drug-sensing and metabolism at the BBB. In porcine BECs, PXR activators, rifampicin and hyperforin. lead to increased expression of *Abcb1* and *Abcg2* mRNA, BCRP and P-gp protein, and P-gp function [182, 183]. These studies provide evidence that activation of PXR and CAR by drugs leads to increased expression and/or function of P-gp at the BBB. With respect to sGC mediated up-regulation of drug transporters, this is likely a coordinated action of GR and PXR/CAR. The sGC dexamethasone is a PXR ligand, and dexamethasone exposure in adult rat brain capillaries leads to increased P-gp protein expression and function [181]. A study conducted in retinal pigment epithelium, which is another protective brain barrier, found that dexamethasone interacts only with GR to up-regulate P-gp, and PXR played a supporting role, potentially through a GR-mediated PXR expression mechanism [178]. Other studies examining the dynamics of GR-PXR activation of P-gp at the BBB and liver do report direct interaction between dexamethasone and PXR, suggesting tissue-specific glucocorticoid responses [177, 184].

Infection/inflammation and the developing BBB

Prenatal exposure to infection and inflammation can disrupt brain development and lead to life-long neurological and behavioral changes [185–191]. Studies in rodents demonstrated that offspring from dams prenatally exposed to infection mimics, including polyinosinic:polycytidylic acid (PolyI:C, a TLR-3 ligand), lipopolysaccharide (LPS, a TLR-4 agonist) and Imiquimod (a TLR-7 ligand) exhibited higher risk of brain injury and adverse neurologic outcomes, including autism, cerebral palsy and schizophrenia [192–199]. Further, viral infection, such as Zika virus and cytomegalovirus [200, 201], also induce adverse neurological outcomes including congenital viral syndrome and microcephaly [202–204]. Recently, it was shown that prenatal maternal exposure to the viral-mimic (PolyI:C) in mice leads to increased accumulation of the P-gp selective substrate [^{3}H]digoxin in the fetal brain at GD15.5, indicating a reduction of P-gp functional activity at the fetal BBB [205]. In this connection, maternal PolyI:C exposure in mid-pregnancy led to long-term offspring motor and cognitive dysfunction [206]. At the placenta, LPS-mediated inflammation impaired P-gp activity and led to greater fetal accumulation of [^{3}H]digoxin at GD15.5 but not at GD17.5 [207], without eliciting changes in placental *Abcb1a/Abcb1b* mRNA [208] and P-gp labyrinthine expression (the exchange site in the mouse placenta). Moreover, maternal infection with *Plasmodium berghei ANKA* (a mouse model of malaria in pregnancy) and Zika virus (ZIKV) in mice, decreased the placental expression of P-gp [209, 210]. Whereas, in the mouse yolk sac, *Plasmodium berghei ANKA* increased *Abcb1a* and P-gp expression[211]. Interestingly, LPS challenge had no effect[212]. Together, these studies indicate that tissue barrier P-gp expression and activity respond differently to specific infective-stimuli and that this response also depends on gestational age, suggesting specific gestational windows of fetal vulnerability to infection and resultant exposure to xenobiotics and environmental toxins.

Previous in vitro studies using porcine and human (hCMEC/D3) BECs derived from adult brains have shown infection and inflammation to inhibit P-gp function [92, 100, 213, 214]. However, little is known as to how infection and inflammation impact P-gp in the developing BBB, and how BCRP and MRPs are affected. In primary cultures of BECs derived from fetal and neonatal guinea pigs at various stages of development, pro-inflammatory cytokines including interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-α induced a dose-dependent inhibition of P-gp function and decreased *Abcb1* gene expression [130]. The magnitude of the effects was highly dependent on the developmental stage at which the BECs were derived. Effects were greatest in cells derived from neonatal animals, were less pronounced in BECs derived from fetuses near term (gestational day (GD) 65; Term ~ GD67), while BECS derived at GD50 (75% gestation) did not respond to pro-inflammatory cytokines [130]. However, a key interaction exists between glucocorticoids and pro-inflammatory cytokines at the level of the developing BBB. In guinea pigs, maternal antenatal treatment with glucocorticoids (single-course dexamethasone at GD50) in vivo, increased P-gp expression and function in the fetal BBB. BECs derived from glucocorticoid exposed fetuses at GD50 demonstrated robust inhibition of P-gp function following cytokine exposure, an effect that was mediated, at least in part by increased cytokine receptor levels [130].

These are important observations because infection is present in 40% of all cases of preterm birth[90], and many of these women will have received prenatal sGC treatment. Given the findings in animal studies, it might be anticipated that sGC treatment of pregnant women might sensitize the fetal brain to the effects of infection, potentially decreasing P-gp-mediated protection of the fetal brain. Clearly, further research is required to investigate this possibility further.

Implications of altered BBB function for neonates

It has been established that fetal BBB function can be modulated by maternal exposure to factors, such as stress, sGC, infection and inflammation. Infants and neonates, particularly those in the neonatal intensive care unit (NICU), represent a vulnerable population who are exposed to a number of drugs, many of which are P-gp and BCRP substrates [215]. Evidently, there are limitations in optimizing drugs for the neonatal population, and its estimated only 35% are FDA approved in neonates. In fact, a large portion of neonatal adverse drug reactions are attributed to agents that target or access the nervous system, such as stimulants (e.g., caffeine), anesthetics (e.g., midazolam), analgesics (e.g., morphine) and antiretrovirals (e.g., Zidovudine). These are some of many agents that are regulated by drug transporters at the BBB, or impact their function [216–218]. In this context, prenatal exposures that lead to long-term changes in BBB function may have consequences for drug efficacy in the post-natal period. There is growing evidence that early life activation of drug-sensing pathways lead to long-term changes in drug metabolism in the liver, effects which are mediated by altered activity and expression of nuclear receptors, such as GR, CAR, and PXR [219]; these same xenobiotic receptors and systems are present at the BBB. If expression and function of drug transporters at the fetal BBB is altered by a prenatal exposure (to glucocorticoids or infection, for example), and these effects persist into post-natal life, this could alter drug uptake in neonates potentially leading to adverse longer-term health outcomes. Understanding how prenatal/post-natal environmental exposures may lead to subsequent post-natal drug interactions is essential to informing the use of these drugs in perinatal care.

Conclusion

Drug transporters, particularly P-gp and BCRP at the developing BBB are crucial for developmental homeostasis and fetal brain protection. Despite their importance, relatively little is known regarding drug transporter regulation in the developing brain, particularly when exposed to environmental factors (e.g., stress, toxins, xenobiotics). There is a key interplay of P-gp and BCRP in fetal brain protection as well as interplay between the placenta and the fetal BBB. In this review, we have highlighted several factors that modulate drug transporters at the developing BBB, including sGC, pro-inflammatory cytokines, maternal infection, and growth factors (TGF-β, Wnt). While some have the potential to increase brain protection (e.g., sGC, TGF-β), others may have profound consequences in increasing xenobiotic exposure (e.g., maternal infection). It is also unknown whether changes at the developing BBB induced by environmental factors will persist into post-natal life. This could have implications for post-natal brain protection, as well as with respect to drug exposure/interactions. The mechanisms underlying these regulatory networks demand further investigation, as well as the potential role of other transporters, including MRPs. Knowledge of the underlying mechanisms of drug transporter regulation at the developing BBB will help to identify potential therapeutic approaches for increasing fetal brain protection.

Author contributions MEE: conceptualization, visualization—figures and tables, writing—original draft. GEI: conceptualization, writing—original draft. EB: conceptualization, writing—review and editing, supervision. SGM: conceptualization, writing—review and editing, supervision, project administration, funding acquisition.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors declare no competing interests.

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