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THE EFFECT OF MATERNAL CREATINE SUPPLEMENTATION IN FETAL NEUROMUSCULAR DEVELOPMENT: A SYSTEMATIC REVIEW

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ABSTRACT
Creatine supplementation is a promising neuroprotective strategy during the perinatal period due to its role in energy metabolism and cellular defense. Preclinical studies have explored its potential to mitigate brain injuries caused by hypoxia, anoxia, and metabolic disturbances. However, variability in study designs and administration protocols necessitates a systematic review of existing evidence. To evaluate the effects of maternal creatine supplementation on neuromuscular development in preclinical studies. A PRISMA-guided review searched Scopus, PubMed, ProQuest, and Cochrane databases (from 2000 up to November 25, 2024) for studies on creatine's effects on brain biomarkers, histopathology, and pathophysiology. Studies using creatine or its derivatives as treatment and reporting experimental outcomes with control comparisons were included. An initial database search identified 346 records. Data were synthesized narratively due to models, outcomes, and dosage heterogeneity. Sixteen studies (2000–2023) involving rodents, sheep, pigs, and cultured fetal tissue were identified. Administration methods included oral, intravenous, intraperitoneal, and ex vivo approaches, with treatment primarily during mid-pregnancy to delivery. Fifteen studies reported significant neuroprotective effects, including biomarker improvements (13 studies) and histopathological changes (3 studies), with no adverse effects noted. Creatine shows potential benefits for fetal neurologic and muscular development, but further research is needed to ensure safe translational application.

Keywords: creatine; development; neuromuscular; pregnancy; supplement

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INTRODUCTION

Perinatal brain injuries, caused by conditions such as hypoxia, anoxia, and metabolic disturbances, remain a significant contributor to neonatal morbidity and long-term neurodevelopmental impairments. Despite advancements in neonatal care, effective preventive and therapeutic interventions are still limited (Chen et al., 2023). Creatine, a naturally occurring compound essential for cellular energy homeostasis, has garnered attention as a potential neuroprotective agent. Widely recognized for its use as a dietary supplement among athletes and individuals engaging in high-intensity exercise, creatine is valued for its ability to enhance muscle performance, replenish ATP, and buffer energy demands during physical stress (Gutiérrez-Hellín et al., 2025; Kreider & Stout, 2021).

Beyond its benefits in sports and exercise, creatine's role in energy metabolism, oxidative stress reduction, and cellular protection has made it an attractive candidate for addressing perinatal neuroprotection. Preclinical studies have investigated maternal creatine supplementation in animal models, demonstrating potential improvements in fetal and neonatal outcomes following perinatal insults (Tran et al., 2025). However, significant heterogeneity in study designs, dosages, administration protocols, and animal models has led to inconsistent findings and challenges in interpretation.

Cerebral palsy is a group of syndromes associated with high mortality, primarily affecting children. While most children with cerebral palsy historically did not survive beyond childhood, advancements in healthcare have extended life expectancy into early adulthood (Paul et al., 2022). The condition arises from non-progressive brain injury occurring in the fetus or infant, leading to various neurological impairments. One significant cause of such injury is birth asphyxia, a major contributor to neonatal morbidity and mortality. Birth asphyxia occurs when blood flow to the placenta is interrupted, resulting in hypoxia and ischemia. If this oxygen deprivation persists for a prolonged period, it can lead to permanent neurological damage, increasing the risk of neurodevelopmental disorders such as developmental delay and cerebral palsy (Su et al., 2024; Techane et al., 2022; Worke et al., 2025). This systematic review aims to synthesize preclinical evidence on maternal creatine supplementation's neuroprotective effects, exploring its impact on neuroprotection and neuromuscular development, which in turn might help prevent the development of cerebral palsy. This review seeks to inform future research and support the clinical translation of creatine supplementation for perinatal care by identifying consistent outcomes and knowledge gaps.

METHOD

This systematic review adhered to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The literature search was conducted across Scopus, PubMed, ProQuest, and Cochrane databases, from 2000 to November 25, 2024, and no limitations on publication dates. MeSH terms and keywords were customised for each database, focusing on three main topics: (1) Creatine; (2) supplementation, therapy; and (3) pregnancy, maternal health. The inclusion process began with consolidating the search results and manually removing duplicate entries. Non-English articles, reviews, protocols, and studies without available translations were excluded. An initial screening of abstracts was carried out independently by a member of the research team (AP) and confirmed by another investigator (DGK). Articles meeting the criteria were retrieved in full text for final evaluation and qualitative synthesis.

The inclusion criteria for articles were as follows: (1) the use of creatine or its derivatives (phosphocreatine, creatine monohydrate, disodium phosphocreatine, or anhydrous creatine) as a treatment, irrespective of dosage, timing, regimen, or administration route; (2) reporting experimental outcomes related to the effects of creatine on brain pathology, behavior, and neurophysiology; and (3) comparison to a vehicle control group. Articles were excluded if creatine was used as part of an adjunct therapy where its independent effects could not be assessed.

Data extraction focused on the general study design (including animal species, sample size, and sex), the preclinical model's age at birth (preterm vs. term equivalent), creatine intervention details (regimen, timing, dosage), and experimental outcomes. Studies evaluating multiple interventions were treated as separate investigations.

Neuroprotection outcomes were assessed through various measures, including (1) functional neurological outcomes evaluated via behavioral, cognitive, sensorimotor, mobility, or electrophysiological tests; (2) histological analyses of brain tissue; and (3) brain metabolism associated with bioenergetic effects. Due to the variability in primary outcomes, timing and dosage of creatine treatments, and differences in preclinical models (age and injury protocols), a meta-analysis could not be performed. Instead, the results are presented as a narrative summary.

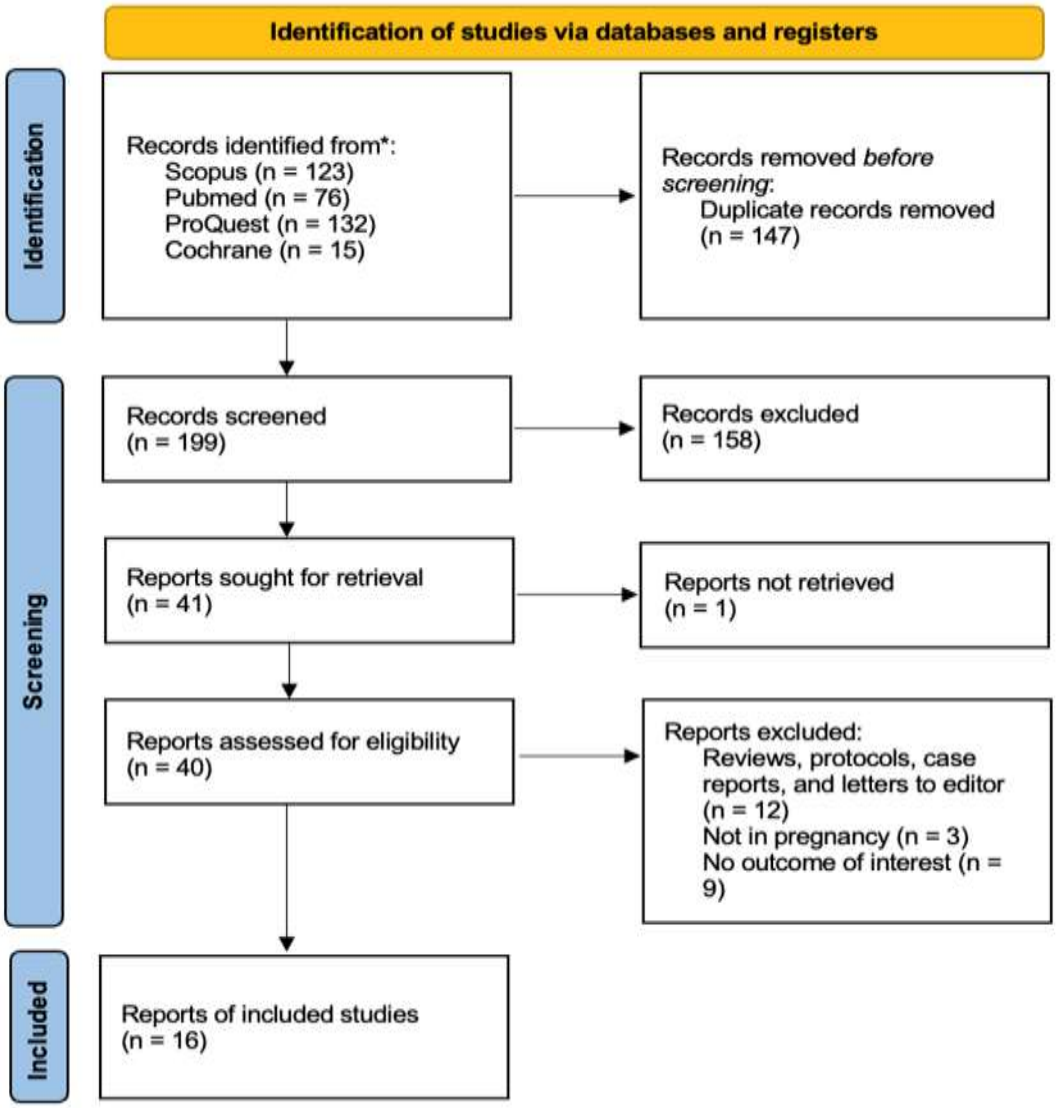

Figure 1. PRISMA search strategy flow chart.

RESULT

The comprehensive search initially identified 346 records. After duplicate removal and screening, 16 articles on creatine supplementation and corresponding outcomes were included in the final analysis (Bortoluzzi et al., 2014; Wilken et al., 2000). The publication year ranged from 2000 to 2023. Twelve studies were conducted in rodents, and seven were conducted between postnatal days. This period (7-20 days postnatal) in rodents is thought to be comparable to human brain development in term or late infancy (Semple et al., 2013). Four studies were conducted in sheep and one in pigs. Ten studies induced anoxia/hypoxia/asphyxia to study the neuroprotective effect of creatine (Cannata et al., 2010; Ireland et al., 2008, 2011; Muccini et al., 2022; Tran et al., 2021, 2023; Wilken et al., 2000). One study induced phenylketonuria (PKU) (Bortoluzzi et al., 2014), and another study induced toxicity using 3-nitropropionic acid (3-NP) (Ducray et al., 2007). Four studies induced no insult and compared the effect of creatine to control groups (Sartini et al., 2016, 2019; Semple et al., 2013; Vallet et al., 2013).

The creatine dosage and administration route varied throughout the studies. Ten studies were conducted using oral maternal creatine supplements, where eight studies put creatine through oral food and two through tap water (Cannata et al., 2010; Ireland et al., 2008; LaRosa, Ellery, Snow, et al., 2016; Sartini et al., 2016, 2019; Semple et al., 2013; Vallet et al., 2013; Wilken et al., 2000). The timing of the supplementation varied, but it mainly started mid-pregnancy up until a day before

or on delivery day. Four studies administered creatine through intravenous access (Ireland et al., 2011; Tran et al., 2021, 2022, 2023). This route was done on sheep, and the creatine was started at the end of pregnancy (121st day gestational age until 134th day gestational age/delivery date). The intraperitoneal route was also done in one study (Bortoluzzi et al., 2014). This route was done for the relatively most prolonged period, ranging from the time of mating up until weaning at the 21st day postpartum. One study's route of administration is undefined since creatine treatment is given to cultured fetal tissue (ex vivo) instead of in vivo (Ducray et al., 2007).

Fifteen out of 16 studies reported at least one significant difference/improvement compared to the control group. Thirteen studies showed an improvement in the levels of biomarkers (Cannata et al., 2010; Ducray et al., 2007; Ireland et al., 2008, 2011; Muccini et al., 2022; Semple et al., 2013; Wilken et al., 2000). Three studies showed improvement through histopathologic comparisons (Bortoluzzi et al., 2014; LaRosa, Ellery, Parkington, et al., 2016; LaRosa, Ellery, Snow, et al., 2016). No adverse effect of creatine supplementation was reported in all studies. Most of the effects were assessed within 24 hours after delivery (Cannata et al., 2010; Ireland et al., 2011; LaRosa, Ellery, Parkington, et al., 2016; LaRosa, Ellery, Snow, et al., 2016; Sartini et al., 2016; Semple et al., 2013; Wilken et al., 2000). Two studies evaluated both at delivery and at adulthood (LaRosa, Ellery, Snow, et al., 2016; Sartini et al., 2016). Two studies only assessed the long-term impact of creatine supplementation in adulthood (Bortoluzzi et al., 2014; LaRosa, Ellery, Parkington, et al., 2016). One study conducted fetal tissue culture at 14 days gestation (Ducray et al., 2007).

Table 1.
Studies of maternal creatine supplementation

Year	Author	Species	Dose	Route	Frequency	Timing	Sample	Time of assessment	Outcome	Insult
2000	(Wilken et al., 2000)	Rats	2 g/kg/d	Oral	Daily	Throughout pregnancy (20 ± 1 day)	Brain tissue	0 d	↑of phosphocreatine in the brainstem higher ATP and phosphocreatine after 30 minutes of anoxia	Anoxia
2007	(Ducray et al., 2007)	Wistar rats	5 mm creatine	-	7 days, 2 days	14 days after vaginal plug	Spinal cord tissue culture	14 days after vaginal plug	↑differentiation of gabaergic neurons Partial significant neuroprotection against 3-NP induced toxicity	3-nitropropionic acid (3-NP) induced toxicity
2008	(Ireland et al., 2008)	Spiny mice	5% creatine monohydrate	Oral (isocaloric pellets	Daily	From d 20 of gestation throught pregnancy	Placenta, kidney, liver, heart, brain tissue	At 37-38 wk gestation	↑Tcr in neonatal placenta ($p<0.001$), brain, heart, liver, and kidney ($p<0.05$). ↑Tcr in maternal liver and kidney. ↑Neonatal survival from hypoxia ($p<0.01$) ↑bodyweight at 15th day postnatal ($p<0.05$)	Hypoxia
2010	(Cannata et al., 2010)	Spiny mice	5% creatine monohydrate	Oral (isocaloric pellets	Daily	From d 20 of gestation throught pregnancy	Diaphgram tissue	24 hr after delivery	↑total creatine in diaphragm ($p<0.05$) ↑diaphragm CSA ($p<0.01$)	Hypoxia
2011	(Ireland et al., 2011)	Spiny mice	5% creatine monohydrate	Oral (isocaloric pellets	Daily	From d 20 of gestation throught pregnancy	Brain tissue	24 hr after delivery	Prevent ↑in apoptosis shown by activated caspase-3 in subplate, thalamus, and piriform cortex ($p<0.05$)	Hypoxia
2013	(Semple et al., 2013)	Spiny mice	5% creatine monohydrate	Oral (isocaloric pellets	Daily	From d 20 of gestation throught pregnancy	Placenta, kidney, liver, heart, brain tissue	24 hr after delivery	No sig. Effect on AGAT or GAMT level in neonatal tissue	None
2013	(Vallet et al., 2013)	Crossbred (Landrace, York, Duroc)	20 g creatine monohydrate	Oral	Daily	110 d GA until birth	Brain tissue	1 d	↑myelin lipids especially in the brainstem	None

Year	Author	Species	Dose	Route	Frequency	Timing	Sample	Time of assessment	Outcome	Insult
		pigs								
2014	(Bortoluzzi et al., 2014)	Wistar rats	0.4 mg of creatine per g of body weight; 0.2 mg of pyruvate per g of body weight	Intraperitoneal	Twice a day (12 hr interval)	At the moment of the mate and continued until weaning of the offspring, at 21 postpartum days	Brain tissue	21 days of age	↓weight reduction at birth and at 21st day. ↓cerebral and hippocampus weight reduction. P<0.01	PKU
2016	(LaRosa, Ellery, Snow, et al. 2016)	Spiny mice	5% creatine monohydrate	Oral (chows)	Daily	From d 20 of gestation throughout pregnancy	Gastrocnemius muscle	24 hr and 33 d	Prevent fiber type changes (p<0.05). Prevent ↓of muscle fiber CSA (p<0.05). Prevent ↓of oxidative capacity in all fiber types (p<0.05). Prevent ↑fatigue caused by repeated contractions (p<0.05)	Hypoxia
2016	(LaRosa, Ellery, Parkington, et al., 2016)	Spiny mice	5% creatine monohydrate	Oral (chows)	Daily	From d 20 of gestation throughout pregnancy	Diaphgram tissue	33 d	↑neonatal survival rate (p<0.01). Prevent muscle fatigue induced by stimulation (p<0.05). Prevent ↑glycolytic fast-twitch fibre (p<0.05). Prevent ↓CSA of all muscle fibre type.	Asphyxia
2016	(Sartini et al., 2016)	Dawley albino rats	1 g/100 ml	Oral (tap water)	Daily	11 d GA to 1 day before delivery	Brain tissue	0 d, 21 d	↑brain creatine levels. ↑brain GSH level. ↑dendritic length.	
2019	(Sartini et al., 2019)	Sprague-Dawley albino rats	1 g/100 ml	Oral (tap water)	Daily	11 d GA to 1 day before delivery	Brain tissue	60 d - 70 d	↑neuron excitability. ↑LTP	None
2021	(Tran et al., 2021)	Border-Leicester/ Merino sheep	6 mg/kg/hr	Intravenous	Daily	121 to 134 d GA	Brain tissue	134 d GA	↑creatine content in cortical grey matter, hippocampus, thalamus, and striatum.	Hypoxia
2022	(Muccini et al., 2022)	Border-Leicester/ Merino sheep	6 mg/kg/hr	Intravenous	Daily	121 to 134 d GA	Brain tissue	134 d GA	Sig. Negative relationship between creatine content in tissue and cell death counts (r =-0.82, p=0.05)	Hypoxia
2022	(Tran et al., 2022)	Border-Leicester/ Merino sheep	6 mg/kg/hr	Intravenous	Daily	121 to 134 d GA	Brain tissue	134 d GA	↓Hydroxyl radixals (OH). ↓Levels of hypoxaemia --> ↓Interstitial cerebral pyrucate, lactate, and OH accumulation	Hypoxia
2023	(Tran et al., 2023)	Border-Leicester/ Merino sheep	6 mg/kg/hr	Intravenous	Daily	121 to 134 d GA	Brain tissue	134 d GA	↓Astroglisosis in corpus callosum ↓cnpase-positive area coverage in the periventricular white matter ↑MBP-positive area coverage in the subcortical white matter	Hypoxia

Hr: hour; d: day; wk: week; sig: significant; GA: gestation age; Tcr: total creatine level; CSA: cross-sectional area; GSH: glutathione; LTP: long term potentiation; AGAT: Arginine-glycine amidinotransferase; GAMT: Guanidinoacetate methyltransferase; MBP: anti-myelin basic protein.

DISCUSSION

This systematic review synthesizes preclinical evidence on the effects of maternal creatine supplementation on fetal and neonatal neuromuscular and neurological development. A total of 16 eligible studies were included after rigorous screening, encompassing various animal models, experimental designs, dosing regimens, and outcome measures. Despite methodological heterogeneity, the overall findings consistently demonstrate that maternal creatine supplementation exerts neuroprotective and myoprotective effects in the developing fetus and neonate, particularly under conditions of hypoxia, anoxia, and metabolic stress (Cannata et al., 2010; Ireland et al., 2008; Muccini et al., 2022; Tran et al., 2021; Wilken et al., 2000).

Neuroprotective Effects of Maternal Creatine Supplementation

One of the most prominent and consistent findings of this systematic review is the neuroprotective effect of maternal creatine supplementation across a wide range of preclinical models. Of the sixteen included studies, fifteen reported at least one statistically significant beneficial outcome in comparison with control groups, underscoring the robustness of creatine's protective potential despite substantial heterogeneity in species, experimental design, dosing regimens, and outcome measures. Collectively, these neuroprotective effects were reflected in improved brain bioenergetics, attenuation of neuronal injury markers, reduction of apoptotic processes, and preservation of neural tissue integrity (Ducray et al., 2007; Ireland et al., 2011; Tran et al., 2023).

At the core of these effects is creatine's well-established role in cellular energy homeostasis. Creatine functions as a phosphate reservoir through the creatine–phosphocreatine system, enabling rapid regeneration of adenosine triphosphate (ATP) during periods of increased energy demand or impaired oxidative metabolism. This mechanism is particularly relevant in the context of perinatal hypoxia–ischemia, where oxygen deprivation disrupts mitochondrial oxidative phosphorylation and leads to rapid ATP depletion. Several studies included in this review demonstrated increased levels of total creatine, phosphocreatine, and ATP in fetal or neonatal brain tissue following maternal creatine supplementation, indicating effective placental transfer and cerebral uptake of creatine (Ireland et al., 2008; Tran et al., 2021; Wilken et al., 2000). The preservation of high-energy phosphate reserves may provide a critical buffer that allows neural cells to maintain essential cellular functions during hypoxic stress.

The importance of these biochemical changes cannot be overstated, as perinatal hypoxic–ischemic insults are characterized by a rapid decline in ATP availability, which initiates a cascade of secondary injury mechanisms. Energy failure leads to membrane depolarization, excessive glutamate release, calcium influx, and subsequent excitotoxic neuronal injury. This process is further exacerbated by mitochondrial dysfunction and the generation of reactive oxygen species, culminating in oxidative stress and cell death. By stabilizing cellular energy metabolism, creatine supplementation may interrupt or delay this pathological cascade, thereby reducing the extent of neuronal damage and limiting long-term neurological impairment.

Beyond its effects on bioenergetics, maternal creatine supplementation appears to modulate cell survival pathways. Multiple studies reported reductions in apoptotic markers, most notably activated caspase-3, in offspring exposed to hypoxic or asphyctic insults (Ireland et al., 2011; Tran et al., 2023). These anti-apoptotic effects were observed in brain regions that are particularly vulnerable during late gestation and the early neonatal period, including the subplate, thalamus, hippocampus, and periventricular white matter. Injury to these regions is strongly associated with adverse neurodevelopmental outcomes, including motor and cognitive impairments. Therefore, the observed reduction in apoptosis suggests that creatine supplementation may play a meaningful role in preserving critical neural circuits during sensitive developmental windows. The attenuation of apoptosis likely reflects both direct and indirect protective mechanisms. Directly, improved ATP availability may prevent the activation of intrinsic apoptotic pathways triggered by energy failure.

Indirectly, creatine's ability to stabilize mitochondrial membranes may reduce cytochrome c release and limit oxidative damage, thereby suppressing downstream apoptotic signaling. Supporting this interpretation, some studies reported inverse relationships between tissue creatine levels and markers of cell death, suggesting a dose-dependent protective effect at the cellular level (Tran et al., 2021, 2023).

Importantly, the neuroprotective effects of creatine were not confined to a single experimental context but were observed across models of hypoxia, anoxia, metabolic toxicity, and even in the absence of an induced insult. This consistency strengthens the biological plausibility of creatine as a broadly acting neuroprotective agent rather than a context-specific intervention. Furthermore, the absence of reported adverse effects across all included studies suggests that enhancement of fetal brain energy reserves through maternal supplementation does not disrupt normal neurodevelopmental processes.

Effects on neuromuscular development and functional outcomes

Beyond its established neuroprotective effects, this systematic review highlights the important role of maternal creatine supplementation in supporting neuromuscular development and functional outcomes in offspring. Several preclinical studies consistently demonstrated preservation of skeletal muscle structure and function in offspring exposed to perinatal hypoxia or asphyxia, including maintenance of muscle fiber composition, prevention of muscle fiber atrophy, preservation of oxidative capacity, and reduced susceptibility to fatigue (Cannata et al., 2010; LaRosa, Ellery, Snow, et al., 2016; Sartini et al., 2016). These findings are particularly significant given the close developmental and functional interdependence between the central nervous system and skeletal muscle during the perinatal period.

Normal neuromuscular development depends on adequate neural input, mitochondrial function, and energy availability. Perinatal hypoxic–ischemic insults disrupt these processes, leading not only to neuronal injury but also to impaired muscle maturation and long-term motor dysfunction. Maternal creatine supplementation appears to mitigate these downstream effects by enhancing energy buffering capacity within muscle tissue, thereby preserving contractile properties and resistance to fatigue. The observed maintenance of oxidative muscle fibers and prevention of shifts toward more glycolytic, fatigue-prone phenotypes suggest that creatine supports metabolic maturation of skeletal muscle under conditions of perinatal stress.

Protection of the diaphragm and limb muscles was a particularly consistent finding across studies involving hypoxic or asphyctic insults (Cannata et al., 2010; LaRosa, Ellery, Parkington, et al., 2016). The diaphragm plays a critical role in neonatal respiration, and its dysfunction can exacerbate respiratory failure in infants with perinatal brain injury. Preservation of diaphragmatic muscle cross-sectional area, fiber type distribution, and fatigue resistance indicates that maternal creatine supplementation may confer functional benefits that extend beyond the central nervous system. Similarly, protection of limb muscles suggests potential benefits for gross motor development, which is frequently impaired in infants with hypoxic–ischemic injury. The clinical relevance of these findings is underscored by the high prevalence of respiratory muscle weakness and motor impairment in neurodevelopmental disorders such as cerebral palsy. Muscle weakness, reduced endurance, and altered fiber composition contribute substantially to morbidity, functional limitations, and reduced quality of life in affected individuals. By preserving neuromuscular integrity during critical developmental windows, maternal creatine supplementation may help reduce the severity of these impairments or improve functional capacity later in life.

Importantly, the benefits of maternal creatine supplementation were not confined to the immediate neonatal period. Several studies extended their assessments into adolescence or adulthood and demonstrated persistent functional and neurophysiological advantages, including enhanced synaptic

plasticity, increased neuronal excitability, and improved long-term potentiation in the hippocampus (Sartini et al., 2016, 2019) Although these outcomes primarily reflect central nervous system function, they are highly relevant to neuromuscular performance, as efficient motor control and coordination depend on intact synaptic connectivity and neural plasticity.

Influence of Timing, Dosage, and Route of Administration

Considerable heterogeneity was observed in creatine dosing regimens, timing of supplementation, and routes of administration across the studies included in this review. This variability reflects the exploratory nature of preclinical research in this field, where optimal dosing strategies and therapeutic windows have not yet been clearly established. Despite these differences, a common pattern emerged in which most studies administered creatine on a daily basis, beginning in mid-pregnancy and continuing until delivery. This supplementation period overlaps with critical phases of fetal brain development, including rapid brain growth, synaptogenesis, and myelination, processes that are highly sensitive to energy availability and metabolic stress (Cannata et al., 2010; Ireland et al., 2008; Tran et al., 2021).

The observation that beneficial outcomes were reported across a wide range of dosages and administration schedules suggests the presence of a relatively broad therapeutic window for creatine supplementation during pregnancy. This finding is particularly important in the context of translational research, as it implies that precise dose titration may not be as critical as ensuring adequate creatine availability during vulnerable developmental periods. The apparent robustness of creatine's effects across experimental conditions also supports the notion that its primary mechanism of action—enhancement of cellular energy buffering capacity—may operate effectively across different exposure levels, provided that tissue creatine concentrations are sufficiently elevated.

Oral maternal supplementation was the most frequently employed route of administration and was consistently associated with increased creatine concentrations in fetal and neonatal tissues. These findings provide strong evidence for effective placental transfer of creatine and support the feasibility of oral supplementation as a practical antenatal intervention (Vallet et al., 2013). The capacity of orally administered creatine to reach multiple fetal organs, including the brain, underscores its potential utility as a systemic neuroprotective strategy rather than a localized or condition-specific treatment. In contrast, intravenous administration was primarily utilized in large-animal sheep models, where it enabled precise control of dosing and timing. Studies employing this route demonstrated particularly robust neuroprotective effects, especially in models of acute global hypoxia, including reductions in cell death, oxidative stress, and structural white matter injury (Tran et al., 2021, 2023).The use of intravenous creatine in these models offers valuable translational insights, as sheep brain development and placental physiology more closely resemble those of humans compared with small rodent models. These findings strengthen the external validity of the observed neuroprotective effects and provide an important bridge between small-animal studies and potential human clinical trials.

Although intraperitoneal and ex vivo approaches were less commonly employed, their inclusion further supports the biological plausibility of creatine's protective effects at the cellular and tissue levels. Intraperitoneal administration, often used in rodent models, allowed for prolonged exposure spanning pregnancy and early postnatal development, while ex vivo fetal tissue studies demonstrated direct effects of creatine on neuronal differentiation and resistance to metabolic toxicity. Together, these approaches complement in vivo findings and reinforce the mechanistic basis for creatine's neuroprotective actions (Gutiérrez-Hellín et al., 2025; Kreider & Stout, 2021).
A particularly notable and clinically relevant finding of this review is the absence of reported adverse maternal, fetal, or neonatal outcomes associated with creatine supplementation, regardless of dose, duration, or route of administration. This consistently favorable safety profile

aligns with existing evidence on creatine use in adult populations, including women, where supplementation has been shown to be well tolerated even with prolonged intake (Gutiérrez-Hellín et al., 2025; Kreider & Stout, 2021). The lack of observed toxicity in preclinical pregnancy models strengthens the rationale for advancing creatine supplementation toward translational and clinical research.

Relevance to Perinatal Brain Injury and Cerebral Palsy Prevention

The findings of this systematic review have important implications for the prevention of perinatal brain injury and its long-term neurological sequelae, particularly cerebral palsy. Hypoxic–ischemic encephalopathy (HIE) remains one of the leading causes of neonatal morbidity and mortality worldwide and is a major contributor to permanent neurodevelopmental disability. Despite advances in neonatal intensive care, effective neuroprotective strategies remain limited. Therapeutic hypothermia, the current standard of care for moderate to severe HIE, has strict eligibility criteria, must be initiated within a narrow postnatal time window, and does not fully prevent adverse neurological outcomes in a substantial proportion of treated infants (Paul et al., 2022). These limitations highlight the urgent need for preventive strategies that can be implemented before injury occurs.

Maternal creatine supplementation represents a fundamentally different and potentially complementary approach to existing postnatal interventions. Rather than attempting to mitigate damage after hypoxic–ischemic injury has already occurred, antenatal creatine supplementation aims to enhance fetal resilience by increasing endogenous energy reserves prior to birth. This preventive strategy is particularly relevant given the unpredictable nature of intrapartum hypoxic events, many of which cannot be anticipated or rapidly addressed in clinical practice. By augmenting fetal brain creatine and phosphocreatine stores, maternal supplementation may enable neural cells to better tolerate acute energy failure during labor and delivery, thereby reducing the extent of primary and secondary brain injury .

The consistent neuroprotective effects observed across diverse preclinical models in this review provide strong support for this prophylactic concept. Improvements in brain bioenergetics, reductions in apoptosis, and preservation of white and gray matter integrity were repeatedly demonstrated in offspring exposed to hypoxia, anoxia, or asphyxia. Importantly, several studies also reported protection of neuromuscular structures, including respiratory and limb muscles, which are critical determinants of functional outcomes in infants with perinatal brain injury (Cannata et al., 2010; LaRosa, Ellery, Snow, et al., 2016). Together, these findings suggest that creatine supplementation has the potential not only to reduce the severity of acute brain injury but also to improve downstream neuromuscular and motor outcomes, which are central features of cerebral palsy .

From a public health perspective, the potential advantages of maternal creatine supplementation are considerable. Creatine is widely available, relatively inexpensive, and has a favorable safety profile in non-pregnant populations. Its oral bioavailability and demonstrated placental transfer in animal models further support its feasibility as an antenatal intervention. In high-risk pregnancies—such as those complicated by fetal growth restriction, placental insufficiency, preeclampsia, or anticipated preterm birth—maternal creatine supplementation could be administered prophylactically to reduce vulnerability to perinatal hypoxic–ischemic insults. If proven effective in humans, this approach could complement existing neonatal therapies and broaden the scope of neuroprotection to include fetuses who may not meet criteria for postnatal interventions.

Nevertheless, despite the promising preclinical evidence, several key knowledge gaps must be addressed before clinical translation can be realized. Most studies included in this review focused

primarily on short-term biochemical, histological, or molecular outcomes, with relatively few assessing long-term functional neurological, behavioral, or cognitive endpoints. Given that cerebral palsy and other neurodevelopmental disorders are defined by functional impairments rather than isolated structural changes, the lack of long-term functional data represents a significant limitation. Additionally, large-animal models that more closely approximate human brain development, placentation, and gestational physiology were underrepresented, potentially limiting the generalizability of findings derived predominantly from rodent studies.

Furthermore, sex-specific effects of maternal creatine supplementation were rarely examined, despite growing evidence that male and female fetuses may differ in vulnerability to hypoxic–ischemic injury and in their neurodevelopmental trajectories. Understanding whether creatine confers differential protection based on sex will be important for optimizing supplementation strategies and interpreting clinical trial outcomes. Addressing these gaps through well-designed preclinical and translational studies is essential to strengthen the evidence base and to inform the design of future human trials.

In summary, the findings of this review position maternal creatine supplementation as a promising antenatal strategy for reducing the burden of perinatal brain injury and potentially lowering the risk or severity of cerebral palsy. While current evidence supports its biological plausibility and neuroprotective potential, further research is required to establish long-term functional benefits, define optimal clinical contexts for use, and ensure safe and effective translation to human pregnancy. This systematic review provides compelling preclinical evidence that maternal creatine supplementation confers neuroprotective and neuromuscular benefits to the developing fetus and neonate, particularly under conditions of hypoxic or metabolic stress. The consistency of beneficial outcomes, combined with the absence of reported adverse effects, supports the potential of creatine as a preventive strategy in perinatal care. While further translational research is required, these findings establish a strong foundation for advancing maternal creatine supplementation toward clinical application.

CONCLUSION

Maternal creatine supplementation shows a promising possibility as a neuroprotective intervention during the perinatal period. Evidence from preclinical studies demonstrates significant benefits, including improved biomarkers, histopathological outcomes, and functional neurological resilience in offspring exposed to perinatal insults. Notably, creatine supplementation was consistently well-tolerated, with no reported adverse effects across the studies reviewed. Despite these encouraging findings, several critical gaps remain, including limited investigation of long-term outcomes and insufficient use of larger animal models reflective of human physiology. Addressing these gaps through robust, translational research is essential to advance creatine from preclinical studies to safe and effective clinical applications. Overall, creatine supplementation represents a compelling avenue for perinatal neuroprotection, offering a potential strategy to mitigate the burden of neonatal brain injuries

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