Special Article

Relationship between arginine intake in parenteral nutrition and preterm neonatal population plasma arginine concentrations: a systematic review

Chandini M. Premakumar, Mark A. Turner, and Colin Morgan

Context: *Very preterm neonates (VPNs) are unable to digest breast milk and therefore rely on parenteral nutrition (PN) formulations. This systematic review was prepared following PRISMA-P 2015 guidelines. For the purpose of this review, desirable mean plasma arginine concentration is defined as* $\geq$*80 micromoles/L.* ***Objective:*** *The review was performed to answer the following research question: "In VPNs, are high amounts of arginine in PN, compared with low amounts of arginine, associated with appropriate circulating concentrations of arginine?" Therefore, the aims were to 1) quantify the relationship between parenteral arginine intakes and plasma arginine concentrations in PN-dependent VPNs; 2) identify any features of study design that affect this relationship; and 3) estimate the target parenteral arginine dose to achieve desirable preterm plasma arginine concentrations.* ***Data Sources:*** *The PubMed, Scopus, Web of Science, and Cochrane databases were searched regardless of study design; review articles were not included.* ***Data Extraction:*** *Only articles that discussed amino acid (AA) intake and measured plasma AA profile post PN in VPNs were included. Data were obtained using a data extraction checklist that was devised for the purpose of this review.* ***Data Analysis:*** *Twelve articles met the inclusion criteria. The dose–concentration relationship of arginine content (%) and absolute arginine intake (mg/(kg* $\times$ *d)) with plasma arginine concentrations showed a significant positive correlation (*$P < 0.001$*).* ***Conclusion:*** *Future studies using AA solutions with arginine content of 17%–20% and protein intakes of 3.5–4.0 g/kg per day may be needed to achieve higher plasma arginine concentrations.*

INTRODUCTION

Human breast milk is the best and ideal form of nutrition for newborn babies, whether full-term or preterm neonates. This is mainly because of the immense immunologic protection obtained from breast milk because immunologic defenses of newborns are not fully developed.[1] However, very preterm neonates (VPNs) are

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unable to tolerate and obtain sufficient feeds to meet nutritional needs due to transient gut immaturity[2] and immature gastrointestinal motor function.[3] This usually occurs in the first few weeks of life, and during this time, VPNs are totally or partially dependent on parenteral nutrition (PN).[4–6] The aims of PN supply are to ensure provision of sufficient energy not only to meet nutritional requirements but also for growth and neurodevelopment.[7] Parenteral nutrition aims to supply nutrients at the same quantity and quality to match the in-utero growth rate of 17–20 g/kg per day weight gain in VPNs[7] and to match the needs of a fetus of the same postconceptional age.[8,9] Increasing survival rates of extremely-low-birth-weight premature neonates has made PN prescriptions more common and widely accepted.[9] However, PN is of interest in this review because previous studies have indicated that current UK-licensed amino-acid (AA) formulations commonly cause hypoargininemia in PN-dependent neonates.[10] Arginine is among many AAs present in an AA solution but it is considered particularly important in the VPN population. This is due to its multiple roles in metabolic and inflammatory pathways as well as it being a major component in body proteins.[10,11] A review article from 2004[12] using neonatal pigs, which is an excellent model for infant nutrition studies, showed that arginine is mainly endogenously synthesized in the intestine of VPNs. However, a more recent study has shown that the kidney is responsible for producing arginine, with small amounts produced by the gut.[13] Very preterm neonates are reported to have immature enzymatic functions in various organs.[12,14] This means there is insufficient production of arginine to meet the growth needs of VPNs.[11] As a result, arginine is a conditionally essential AA in VPNs, requiring exogenous supply. This deficiency is further aggravated by the increased demand for arginine in preterm infants due to the multiple uses of arginine via various pathways, such as for growth, ammonia detoxification, insulin secretion, precursors for synthesis of nitric oxide, creatine, and polyamines, which affect cardiovascular, pulmonary, immunological, intestinal, and neurological function.[12,14] Collection of evidence from various human studies from the 1970s to the 1980s[15–20] suggests that PN-induced low plasma arginine concentrations are associated with hyperammonemia. Interestingly, studies supplementing preterm infants with exogenous intravenous L-arginine indicate that hyperammonemia can be prevented and preterm morbidities, such as necrotizing enterocolitis (NEC) and persistent pulmonary hypertension, can be reduced.[11,12,18,21,22] However, AA formulations that are widely used in the United Kingdom have not been changed in the last 25 years to address these issues.[10] This comes as a surprise because, although there are technical reasons such as insolubility or instability that limit the addition of other conditionally essential AAs such as tyrosine, cysteine and glutamine, there are no technical barriers for arginine supplementation. In fact, there are AA solutions with much higher arginine content than those used in the United Kingdom. A US-licensed AA formulation known as TrophAmine 10% (BBraun)[23] contains 12% arginine compared with Vaminolact 6.5% (Fresenius Kabi)[24] and Primene 10% (Baxter),[25] which only have 6.3% and 8.4% arginine, respectively. Regrettably, plasma AA profile monitoring is not a routine monitoring parameter in clinical practice, despite progressively earlier and higher parenteral AA doses being used/recommended in most neonatal units.[11]

To date, there are no reviews about the relationship between arginine intake and its plasma concentration and also no recommended threshold intake of arginine to achieve desirable plasma arginine concentrations. For the purpose of this systematic review, desirable mean plasma arginine concentration was set as $\geq$80 micromoles/L. This value was based on plasma arginine associations with clinical conditions from the literature[26,27] and recognizes the lack of consensus on values considered to be acceptable normal plasma arginine concentrations in this population.[28] Previous published studies have quoted various ranges of target plasma AA and arginine concentrations for the VPN population based on different reference groups. Commonly used plasma arginine concentrations (mean $\pm$ SD) are from healthy term breast-fed infants with postnatal age between 28 and 32 days (95.3 $\pm$ 24.9 micromoles/L; range of 42.3–148.2 micromoles/L)[29]; healthy term breast-fed infants with postnatal age of 11 days (55 $\pm$ 21 micromoles/L; range 11–88 micromoles/L)[30]; preterm unsupplemented breast milk (69 $\pm$ 20 micromoles/L)[31]; cord blood AA concentrations from neonates of 29 weeks' gestation (82 $\pm$ 55 micromoles/L)[32]; or low-birth-weight infants receiving TrophAmine (88.6 $\pm$ 40.6 micromoles/L).[33] Reference plasma arginine concentrations range from a lowest value of 11 micromoles/L to a highest value of 148 micromoles/L. A pragmatic mean plasma arginine concentration target of $\geq$80 micromoles/L is used in this review. This choice is based on a middle point of all the commonly used plasma arginine concentrations quoted above. Furthermore, studies have shown that babies with mean plasma arginine concentration >80 micromoles/L have lower incidences of NEC and lower plasma ammonia levels.[12,26,27]

The research question addressed in the present review is: "In VPNs, are high amounts of arginine in PN, compared with low amounts of arginine, associated with appropriate circulating concentrations of arginine?" Hence, in order to optimize PN formulation

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Population	Intervention	Comparison	Outcome	Study Design
• Parenteral nutrition–dependent very preterm neonates • Total parenteral nutrition • Intravenous feeding • Hyperalimentation • Intravenous alimentation • Intravenous nutrition • Parenteral alimentation • Parenteral hyperalimentation • Dietary supplements • Infant Nutritional Physiological Phenomena • Infant Food • Human • Infants • Neonates • Preterm • Premature	• High amounts of arginine • Arginine • Amino acids • Essential amino acids • Conditionally essential amino acids	• Low amounts of arginine	• Plasma amino acid • Aminogram • Blood amino acid levels	All study designs except review articles

design with respect to arginine content, this systematic review prepared according to PRISMA-P 2015 guidelines uses available evidence from the literature: 1) to quantify the relationship between arginine intake as percentage content (%) and absolute intake (mg/(kg × d)) with plasma arginine concentrations in PN-dependent VPNs; 2) to identify any features of study design that affect the relationship between arginine intake and plasma arginine concentrations; and 3) to estimate the target threshold arginine dose to achieve target mean plasma arginine concentrations of ≥80 micromoles/L in the same population.

METHODS

This review was prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 (see Appendix S1 in the Supporting Information online). Adaptations from systematic reviews used by Cochrane Collaboration[34] and other resources[35,36] were used as a methodology guide.

Search strategy

Individual search strategies were designed for PubMed, Scopus, Web of Science, and Cochrane databases using the PICOS (Population, Intervention, Comparison, Outcome, Study design) formula. The research question, "In VPNS, are high amounts of arginine in PN (expressed as percentage or absolute amount), compared with low amounts of arginine (expressed as percentage or absolute amount), associated with appropriate circulating concentrations of arginine?" was broken down into main concepts (Table 1).

Study inclusion and exclusion criteria

Using the concepts and a combination of medical subject heading (MeSH) terms and keywords as shown in Table 1, the search was performed on all of the databases with no cutoff on publication date. This review excluded studies that were not reported in the English language; review articles with no original data; studies that did not include human participants who were ≤32 weeks' gestational age at birth and within 28 days of life; studies for which the type of AA solution used as part of PN regimens was not reported; studies for which protein or AA intake per day was not reported; studies for which plasma AA profiles, specifically arginine concentrations, were not reported; studies that supplied PN to patients for a duration <5 days; and studies for which only plasma AA concentrations in the first 3 days of life before maximum PN intake is usually achieved were reported. Wherever information was not clear or explicitly mentioned in the article, study authors were contacted directly for extra information. The search strategy used on the Scopus database is described in Table 2.

Selection of studies

The results of the search were narrowed down as illustrated in Figure 1. Each phase of the study selection process occurred in 2 stages. It was done thoroughly by the principal researcher before being double-checked by 2 additional independent researchers to establish reliability.

Data extraction

Following piloting, data collection was performed using a data extraction form (see Figure S1 in the Supporting

Table 2 **Scopus search strategy**

Database searched: Scopus	Components of research question and keywords			
	Concept 1: Population	Concept 2: Population	Concept 3: Intervention	Concept 4: Outcome
Boolean operators	**AND**	**AND**	**AND**	**AND**
OR	Parenteral nutrition	Infant[a]	Arginine	Plasma amino acid level[a]
OR	Total parenteral nutrition	Preterm	Amino acid[a]	Plasma amino acid[a]
OR	Parenteral nutrition solution[a]	premature	Essential amino acid[a]	Aminogram[a]
OR	Dietary supplement[a]		Condition[a] essential amino acid[a]	Amino acid level[a]
OR	TPN			Plasma amino acid value[a]
OR	PN			Amino acid value[a]
OR	Intravenous feed[a]			
OR	IV feed[a]			
OR	Hyperalimentation			
OR	Intravenous alimentation			
OR	Parenteral alimentation			
OR	IV alimentation			
OR	Intravenous nutrition			
OR	IV nutrition			
OR	Parenteral hyperalimentation			

[a]Truncation; the "TITLE-ABS-KEY" field code was used.

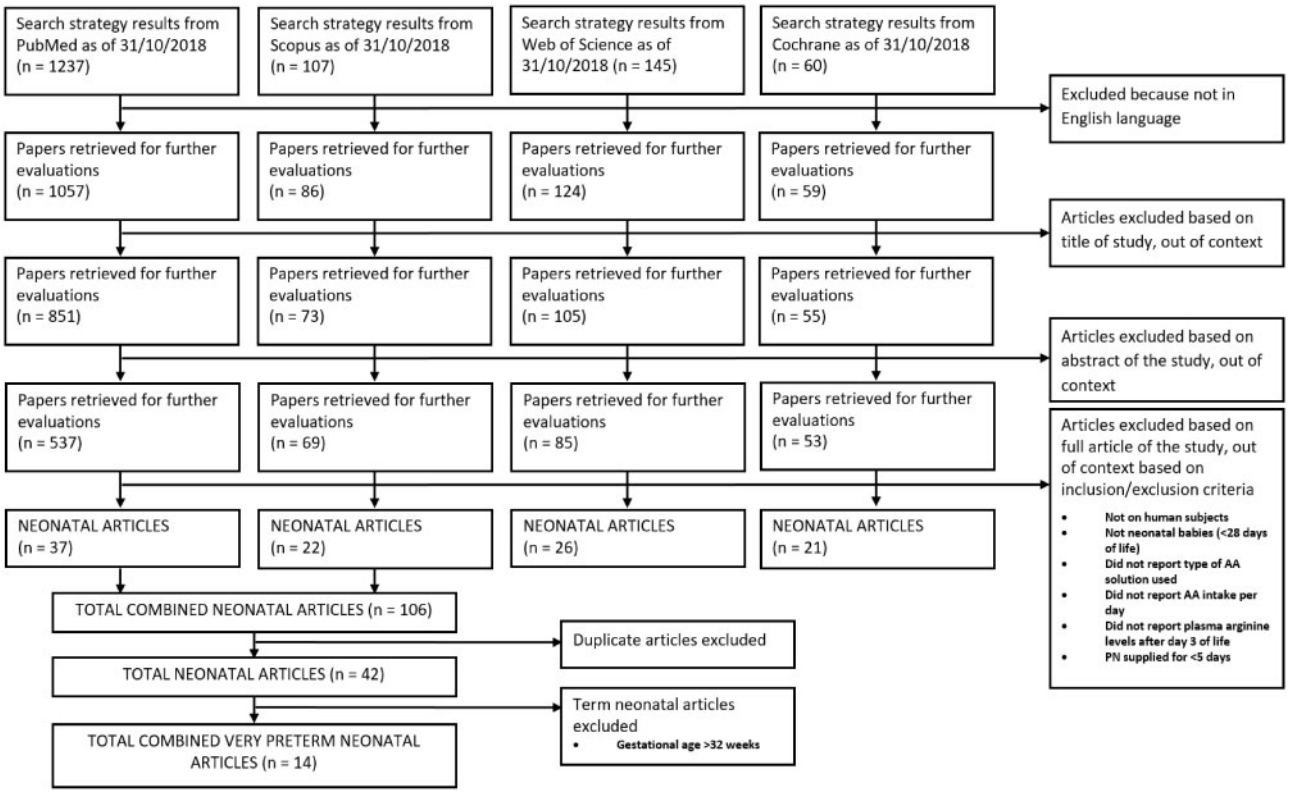

Figure 1 **Flow diagram of the literature search process**. *Abbreviations:* AA, amino acid; PN, parenteral nutrition.

Information online). This was done independently by 3 researchers, and data were stored on Microsoft Excel spreadsheets.

The main outcome being assessed in this review is the plasma arginine concentrations of VPNs. This was to establish a relationship between the arginine intakes with the plasma concentrations and thereafter predict arginine intake to achieve target plasma concentrations. Secondary outcomes included type of study design, type of AA intake reported, and type of AA analysis

technique used. These were used in studying possible bias factors that affected the primary outcome(s) of the included studies.

Quality assessment of each study was performed using a quality assessment tool to evaluate and identify risk of bias of the individual studies. This was done at the study level using the quality assessment tool, whereas at the outcome level the risks were assessed against possible identified bias factors. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework was also used to assess the quality of the outcome reported for the studies included in this systematic review.

Throughout the review process, any points of disagreement, such as simple oversights and differences in interpretation, were discussed and, where possible, resolved by consensus after referring to the protocol. Disagreements due to lack of information were resolved by contacting the study authors for clarification.

Statistical analysis

There was high data variability among the groups within individual studies because the studies were not assessing plasma AA concentration as a primary outcome. There was also high clinical heterogeneity among the various studies as a result of inclusion of studies from various clinical settings and years with differences in local practice guidelines. These structural reasons for heterogeneity made the data unsuitable for meta-analysis. If data had been more homogenous, advanced statistical tests such as meta-analysis, forest plots, and meta-regression could have been performed. Basic statistical tests of the data were done using SPSS 22 software (SPSS Inc, Chicago, IL, 2013)[37] to produce scatter plots as well as perform correlation and regression analyses where appropriate. Subgroup analysis was also performed based on type of chromatography method used for plasma AA analysis. No assessment of meta-bias was planned as part of this review.

RESULTS

Data characteristics

There was a total of 37 articles from PubMed, 22 articles from Scopus, 26 articles from Web of Science, and 21 articles from Cochrane that focused on the neonatal population; however, 64 articles were duplicates. Hence, the cumulative total number of neonatal articles was 42. Of these, 14 articles focused on VPNs (defined as $\leq$32 wk gestation), although 2 of these articles[28,38] are not discussed in this review (Figure 1). Thus, this review focuses on 12 articles, 11 of which reported on randomized controlled trials (RCTs) and 1 reported on a non-RCT study.

There were a total of 798 VPNs, which included both males and females with minimum and maximum gestational ages of 24 and 32 weeks', respectively. Sample sizes ranged from as small as 15 to as high as 152 neonates. Summarized results are presented in Table 3.[10,21,39–48]

Evaluation of the dose–concentration relationship

There was a positive correlation between the percentage arginine content and plasma arginine ($r = 0.814$, $n = 23$, $P \leq 0.001$), as well as between absolute arginine intake and plasma arginine ($r = 0.740$, $n = 23$, $P \leq 0.001$). The correlation between percentage arginine content and plasma arginine is stronger than between absolute intake and plasma arginine concentrations.

A simple linear regression was calculated to predict plasma arginine concentrations based on percentage arginine content in AA solutions. A significant regression equation was found ($F(1, 21) = 41.145$; $P < 0.001$), with an R^2 of 0.662. The predicted plasma arginine concentrations (micromoles/L) of VPNs is equal to $2.182 + 8.275 \times$ proportion arginine content (%). Plasma arginine of VPNs increased by 8.275 micromoles/L for each percentage increase of arginine content. The same was done to predict plasma arginine concentrations based on absolute arginine intake. A significant regression equation was found ($F(1, 21) = 25.466$; $P < 0.001$), with an R^2 of 0.548. The predicted plasma arginine concentrations (micromoles/L) of VPNs is equal to $11.191 + 0.247 \times$ absolute arginine intake [mg/(kg $\times$ d)]. Plasma arginine concentrations of VPNs increased by 0.247 micromoles/L for each mg/(kg $\times$ d) increase in absolute arginine intake. These findings are illustrated in Figure 2.

A multiple linear regression was calculated to predict plasma arginine concentrations based on percentage arginine content in AA solutions and absolute arginine intake. A significant regression equation was found ($F(2, 20) = 23.384$; $P < 0.001$), with an R^2 of 0.7.

The predicted plasma arginine concentrations (micromoles/L) of VPNs is equal to $-4.074 + 6.010 \times$ proportion arginine content (%) $+ 0.099 \times$ absolute arginine intake [mg/(kg $\times$ d)]. The plasma arginine concentrations of VPNs increased by 6.010 micromoles/L for each percentage increase of arginine content and 0.099 micromoles/L for each mg/(kg $\times$ d) increase in absolute arginine intake. However, only percentage

Table 2 **Characteristics of the 12 studies included in this systematic review**

Reference	Sample size	Gestational age, wk	Postnatal age	Amino-acid solution	Arginine content, %	Estimated average arginine intake, mg/kg per day	Plasma arginine concentrations, micromoles/L
Chessex et al (1985)[40]	15	28 ± 1	14 ± 5 d	Travasol 10% blend B vs Vamin 7%	1a: 10.4%; 1b: 4.7%	1a: 270.4; 1b: 150.4	1a: 124 ± 46; 1b: 83 ± 28
Mayes et al (2014)[46]	118	2a: 26 ± 1.5; 2b: 26.2 ± 1.5	Within first 7 d of age	Primene 10%	2a: 8.40%; 2b: 8.40%	2a: 277.2; 2b: 235.2	2a: 51 (30–75); 2b: 46 (26–65)
Bulbul et al (2012)[45]	44	3a: 29.4 ± 1.8; 3b: 29.1 ± 1.1	3a: 5.3 ± 2.5 h; 3b: 4.6 ± 2.2 h	Primene 10%	3a: 8.40%; 3b: 8.40%	3a: 302.4; 3b: 302.4	3a: 73.5 ± 27; 3b: 85.0 ± 70.2
Blanco et al (2011)[44]	61	4a: 26.3 ± 2; 4b: 25.7 ± 2	4a: 6.6 h; 4b: 30.6 h	Aminosyn PF 10%	4a: 12.30%; 4b: 12.30%	4a: 361.6; 4b: 477.2	[a]4a: 108.8 (61.3–210.2); [a]4b: 115.8 (66.9–209.7)
Amin et al (2002)[21]	152	5a: 27.4 ± 0.3; 5b: 27.6 ± 0.2	Between days 2 to 5	TrophAmine 3%	5a: 19%; 5b: 12%	5a: 398 5b: 181	5a: 158 (8); 5b: 88 (6)
Poindexter et al (2003)[42]	141	6a: 26.3 ± 1.8; 6b: 26.2 ± 2.0	Before 72 h of age	TrophAmine 10%	6a: 12%; 6b: 9.6%	6a: 262.8 6b: 230.4	6a: 73 (56-107); 6b: 62 (45-112)
Ng et al (1992)[48]	59	7: 27 ± 2	Day 2 of life	Vamin 9 glucose	7: 4.70%	7: 141	7: 21 ± 2
Ogata et al (1983)[39]	17	8a: 28.2 ± 0.7; 8b: 28.0 ± 1.6	Within 24 h of birth	Neopham vs Aminosyn	8a: 9.9%; 8b: 6.3%	8a: 266.3 8b: 161.3	8a: 88 ± 34; 8b: 55 ± 30
Kalhan et al (2005)[43]	20	9a: 27.7 ± 2.0; 9b: 26.7 ± 1.6	Between day 1 and day 2 after birth	TrophAmine 10% vs TrophAmine 10% glutamine	9a: 12%; 9b: 9.6%	9a: 396 9b: 316.8	9a: 96.9 ± 45.2; 9b: 76 ± 29.8
Morgan and Burgess (2017)[10]	126	10a: 26.8 ± 1.3; 10b: 26.6 ± 1.4	Within 48 h after birth	Vaminolact 6.5%	10a: 6.30%; 10b: 6.30%	10a: 224 10b: 186	10a: 41 (25–57); 10b: 35 (22–46)
[c]Mitton et al (1993)[41]	29	11a: 29 ± 3; 11b: 29 ± 2	Before 4 d postnatal age	Vamin 9 glucose vs Vamin Infant	11a: 4.7%; 11b: 6.3%	11a: 150.4 11b: 195.3	[b]11a: 43 (10–88); [b]11b: 77 (12–112)
Balakrishnan et al (2017)[47]	16	[d]12a: 26.6 (24–30) [d]12b: 26.9 (24–30)	Within 18 h of delivery	Premasol 10% (similar to TropAmine)	12a: 12%; 12b: 12%	12a: 456 12b: 444	12a: 140.9 ± 52.8; 12b: 100.6 ± 22.3

Results are expressed as mean ± standard deviation; mean (standard error of mean); or median (Q_1–Q_3) unless otherwise indicated.
[a]Median (10^{th} to 90^{th} percentile).
[b]Mean (95% confidence interval).
[c]Gestational age not specified, but the majority of babies will be <33 weeks based on reported mean ± standard deviation gestational age of babies recruited.
[d]Median (Q_1–Q_3).

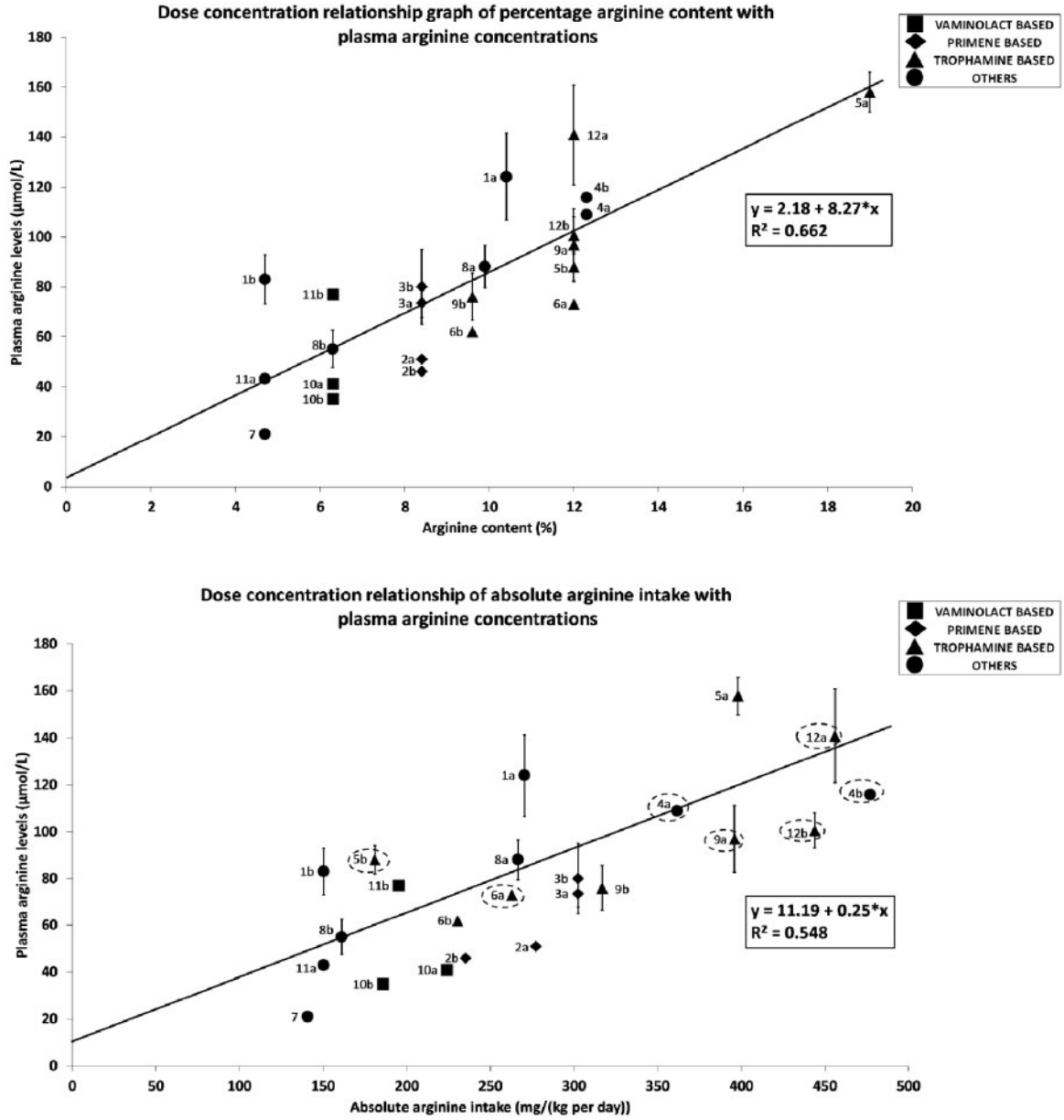

Figure 2 **Dose–concentration graphs of arginine content as percentage and absolute intake with plasma arginine concentrations.** Each point of the graph represents the study group from each article; study is coded based on amino-acid solution used in the parenteral nutrition. a) Arginine intake represented as percentage arginine content on the x-axis. b) Arginine intake represented as absolute arginine intake, which was obtained by multiplication of arginine content in percentage with the amino-acid intake of the neonates. Refer to Table 3 for identification of study point labels. Circled points refer to solutions that have an arginine content of 12.0%–12.3% with varying protein intakes.

content of arginine is a significant predictor ($P = 0.005$) of plasma arginine concentrations in this model, reinforcing the previous finding that percentage arginine content has a stronger correlation with plasma arginine concentrations.

Because there was a correlation between arginine as percentage content with absolute intake, an interaction term was considered and analyzed in the regression model, which then appeared significant ($P < 0.001$) in the model prediction.

Analysis of bias factors and quality assessment

The study groups that used ion-exchange chromatography (n = 13) had lower plasma arginine concentrations (M = 72.04; SD = 41.1) than the groups that used high-performance liquid chromatography (n = 8; M = 94.75; SD = 19.5). However, the difference was not statistically significant ($t(19) = -1.5$; $P = 0.2$).

The use of a quality assessment tool gave evidence that more than half of the studies did not have a clearly

formulated hypothesis. Furthermore, 25% of the articles did not describe the duration of PN clearly, and approximately half of the articles did not describe either instruments or techniques used in plasma AA analysis clearly. Although most studies considered adverse event monitoring and reporting, only one third of the studies measured and reported baseline monitoring data. The findings suggest there is a fair amount of variation in data collection and data reporting for studies in this research area. Based on GRADE assessment, the overall quality of the body of evidence would be categorized as low.

DISCUSSION

This systematic review summarizes the relationship between arginine intake and plasma arginine concentrations in VPNs based on evidence from previous studies. Although these studies did not aim to link arginine intake with its plasma concentrations as a primary outcome, the relevant information was available from these articles and thus could be used to clearly define the relationship between the two. This approach has the potential to identify a threshold arginine intake required to achieve desirable plasma arginine concentrations. Two of the 14 initially included studies articles were not analyzed because the plasma concentrations were based on data from 2 different AA solutions rather than on a single AA solution.

The correlation coefficients and regression equations from the results section and Figure 2 in the present review suggest that arginine content as a proportion (%) was a marginally better predictor of plasma arginine values compared with absolute arginine intake (mg/(kg × d)).

This could be due to many reasons; however, most of these reasons are speculative because of the difficulty in quantifying metabolic needs for each AA in VPNs and how they are used. Arginine needs are largely defined by protein synthesis and, to a smaller extent, by metabolic routes such as ammonia removal, synthesis of nitric oxide, and various other molecules. There is a minimum requirement for each AA, and the contribution of arginine is thought to be more important[12,49,50] because arginine is the most abundant nitrogen carrier, containing 4 nitrogen atoms per molecule.[51,52] However, the specific requirements of arginine for metabolic processes are unknown. The need to meet the increased metabolic demands of VPNs for arginine may mean less arginine would be available for protein synthesis. It is difficult to quantify these needs due to the complexity of this highly active system, as well as varied demands of neonates. Nevertheless, because 12%–18% of total free AA nitrogen composition in porcine amniotic fluid during early gestation is made up of arginine,[51,53] it is assumed that similar quantities of arginine would be needed to meet the demands of VPNs. However, none of the existing AA solutions in the United Kingdom provide this amount. The only real measure of arginine utilization would be to evaluate protein synthesis. However, protein synthesis impairment could be due to insufficiency of arginine and/or other AAs. The data suggest that arginine demands already seem to exceed the amounts provided via PN formulation. Furthermore, due to the lack of enteral synthesis of arginine from digested milk protein, deficiency would seem inevitable in most VPNs. Measuring functional deficiency indicators such as plasma ammonia concentrations, which have a well-established link with arginine concentrations, is one approach to identify low plasma arginine concentrations that are clinically important. However, once again it is not known how sensitive ammonia is as a measure of arginine deficiency.

The graphs in Figure 2 reiterate the statistical finding that percentage arginine content is a more notable predictor of plasma arginine concentrations. The points on the bottom panel of Figure 2—specifically, for Aminosyn PF 10% with arginine content of 12.3% (data points 4a and 4b), as well as TrophAmine (coded Δ) with 12% arginine content, except points 6b and 9b—have been analyzed separately in more detail (all dotted circle points). All of these points have similar arginine content in the PN solution as a proportion and hence the *x*-axis is not just reflective of absolute arginine intake it, also acts as a surrogate marker for total protein intake across these points. These points, except for point 12a, report plasma concentrations of approximately 80 micromoles/L (ranging from 73 to 115.8 micromoles/L), which was the target mean plasma arginine level for this review. The reason points 6b and 9b were not included as part of the above analysis is because, although those points were for TrophAmine, the patients in those groups did not receive AA solutions with arginine content of 12% due to the study design, which included glutamine supplementation without increasing the overall protein or nitrogen content of the AA solution.

There are more data points in Figure 2 for percentage arginine content up to approximately 12% and absolute arginine intake up to approximately 350 mg/(kg × d). However, there are fewer points at the higher end and those few points have very different protein intakes, hence making it a little more difficult to interpret the higher end of the graph. Study points with lower AA intake but higher PN arginine content reported higher plasma arginine concentrations than points with higher AA intake but lower PN arginine content. This may imply that when VPNs are given a

higher protein intake, the extra arginine supplied may actually be utilized more effectively for growth whereas VPNs that do not receive high enough protein intake may end up with excess arginine in the blood. This also suggests that protein intake probably has a big impact on the higher end of the graph, and therefore more studies are needed to explore the higher end of the graph intake to provide a clearer understanding.

Current guidelines suggest AA supply to be given early (within first postnatal day with at least 1.5 g/kg/d) and high at 2.5–3.5 g/kg/d from postnatal day 2 onwards in premature neonates.[54] Survey findings show that >80% of units in 4 European countries (the United Kingdom included) achieve target AA intake of 3–4 g/kg/d.[55] Therefore, if more arginine is supplied as percentage content in AA solutions, better utilization of arginine, as well as improved plasma arginine concentrations, may be achievable. The above findings are very important and useful in terms of formulation design because they indicate a higher proportion of arginine is required in currently licensed AA solutions based on the AA intake a VPN receives to achieve higher plasma arginine concentrations.

The type of study was intended to be examined as a potential source of bias, but only 1 of the included articles was a non-RCT study. Similarly, only 1 article reported prescribed and not actual AA intake. Therefore, it is not possible to comment on the potential bias arising from study design or AA intake. Visual analysis of scatter plots suggests the type of AA analysis method appeared to have an effect on the dose–concentration relationship despite no statistical significance between the measurements. The variation in characteristics of participants, as well as the analytical method, may produce variability in the plasma concentrations, in addition to difference in accuracy of various analytical methods.[56]

The variation in data collection and reporting of the studies makes data compilation and comparative analysis challenging because there are not very many articles that report similar outcomes that have been considered to be important. The quality assessment tool used for the purpose of this review could be used as a guide for future studies in the research field of parenteral nutrition among VPNs (Figure 3).

The risk of bias was moderate based on GRADE assessment; although 11 of 12 articles in the review were RCTs, only 5 clearly explained the study design. There was high inconsistency among the various studies included in the review because the primary outcomes were diverse and because there are not many neonatal nutrition studies that had plasma AA data as the primary outcome. There is also high imprecision in the outcome due to the wide range of reference values reported for the plasma arginine values and used in the various studies. There are low levels of indirectness because articles included in the review focused on the target population and reported the outcome of interest although it may not have been the primary outcome of the original study. Publication bias is considered moderate because there are some early studies (1980s) included with small sample sizes. Additionally, there could be studies that were not published due to null results, and thus these studies were not captured in the selection process. Such publication biases are unresolvable but need to be recognized as possible contributors to publication bias. The thorough methodology of the present review reduced the possibility of publication bias of the studies included.

Confidence in the body of evidence was rated up wards due to the dose–concentration relationship. Overall, the evidence is not sufficiently robust to imply changes in policy making or clinical practice. Further studies are needed to increase the value of the evidence found. Therefore, the quality of the body of evidence would be categorized as low based on the points mentioned above.

Strengths and limitations

The strength of this review's approach is the ability to indirectly identify and measure arginine deficiency by means of functional deficiency indicators such as plasma AA and ammonia concentrations, which will be able to provide information on arginine needs for VPNs. However, this approach remains speculative, and there are limitations in focusing on 1 metabolic pathway (urea cycle) that is dependent on other AAs and non-nutritional factors such as enzyme immaturity. Furthermore, plasma arginine levels are mainly reflective of protein synthesis rather than the hepatic urea cycle.

This review considered mean plasma values >80 micromoles/L as desirable plasma arginine concentrations based on interpretation of published studies. Nevertheless, it is not certain if this is the best target concentration, especially because the only clinical study[21] so far to have shown that arginine supplementation reduces NEC in premature infants reported plasma concentrations of approximately 160 micromoles/L (point 5a on Figure 2) on day 14 of life. Therefore, it is possible that target plasma arginine concentrations need to be as high as that to get the clinical benefit of NEC protection from arginine supplementation. This could suggest that 80 micromoles/L might be the minimum normal plasma arginine value. However, these

QUESTIONS		1	2	3	4	5	6	7	8	9	10	11	12	Percentage score per question
1. Internal validity	1.1 Title summarises the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	1.2 Abstract: structured?	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	81.8%
	1.3 Abstract: provide clear summary of the study?	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	100.0%
	1.4 Are funding sources identified?	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	66.7%
	1.5 Are any potential conflicts of interest identified and adequately explained?	N	N	Y	Y	N	Y	N	N	N	N	N	Y	33.3%
	1.6 Introduction/background:													
	- population clearly identified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	- incidence of condition that caused need for PN?	N	N	N	N	Y	N	N	N	N	N	N	N	8.3%
	- driver for this study identified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	1.7 Objective/aim clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	1.8 Were eligibility criteria for participants clear?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	91.7%
	1.9 Were rejection criteria stated clearly?	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	66.7%
	1.10 Clear rationale for the selection of PN/AA solution given?	N	N	N	Y	N	N	Y	Y	N	N	Y	N	33.3%
	1.11 Was ethical approval obtained and described clearly?	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	75.0%
	1.12 Were patient's consent obtained and reported clearly?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	91.7%
	1.13 Were any co-existing conditions in patients reported?	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	N	58.3%
	1.14 Were baseline data obtained and reported?	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	66.7%
	1.15 Were any additional AA supplementation described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	1.16 Were adverse events considered?	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	75.0%
	1.17 Were adverse events clearly reported?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	83.3%
2. Methods	2.1 AA solution given?													
	- brand name	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	- strength (%)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	91.7%
	- composition/content	N	N	N	N	N	N	N	Y	Y	Y	Y	N	33.3%
	- manufacturer/company	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	2.2 Primary aim/purpose of the study clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	2.3 Any secondary aims clearly stated?	Y	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	Y	100.0%
	2.4 Hypothesis clearly stated?	N	Y	Y	N	N	Y	N	N	N	Y	N	Y	41.7%
	2.5 Sample size determination completed?	N	Y	Y	N	Y	N	N	N	N	N	N	Y	33.3%
	2.6 Non-protein sources clearly described?	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	75.0%
3. Randomisation	3.1 Sequence generation explained?	N	Y	Y	Y	N	Y	NA	N	N	N	N	Y	45.5%
	3.2 Allocation concealment described?	N	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	72.7%
	3.3 Blinding of participants, personnel and outcome assessors mentioned?	N	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	72.7%
4. Crossover studies	4.1 Has the order of receiving treatments been randomised?	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100.0%
	4.2 Was it clear how many treatments or periods were being used?	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100.0%
	4.3 Was a suitable wash-out period used?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	4.4 Were drop-outs reported and considered acceptable?	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100.0%
	4.5 Paired analysis completed?	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100.0%
5. Manipulation	5.1 Was the AA solution clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	5.2 Was the route of AA supply described? (peripheral, central, etc)	Y	N	Y	N	N	N	N	Y	N	N	N	N	25.0%
	5.3 Was the duration of the provision of TPN/AA solution clearly described?	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	75.0%
	5.4 Was the day of plasma AA analysis clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	5.5 Were there any other additional sources of nutrition explained? (Formula/oral?)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	91.7%
	5.6 Were the actual intakes described?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	91.7%
6. Measurement methodology	6.1 Has the measurement methodology been reported as validated or used previously?	Y	Y	N	N	Y	N	N	Y	Y	Y	N	N	50.0%
	6.2 Could it be repeated?	Y	N	Y	Y	Y	Y	N	N	Y	N	Y	N	58.3%
	6.3 Were the type of blood sample described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	6.4 Were the instruments used to measure outcome defined clearly?	Y	N	Y	N	Y	Y	Y	N	N	N	Y	Y	58.3%
	6.5 Were the technique used to measure outcome defined clearly?	N	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	58.3%
	6.6 Was there complete data reporting?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	6.7 Were confounding factors identified?	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	75.0%
	6.8 Were confounding factors taken into account of study design/analysis?	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	75.0%
	6.9 Were patients followed up for long enough?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
7. External validity	7.1 Are the results and conclusions relevant to the aims/objectives of the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	7.2 Are results critically appraised in relation to previous work?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	91.7%
	7.3 Are the results applicable to population of concern?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	7.4 Does the study demonstrate:													
	- proof-of-concept	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0%
	- efficacy	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	91.7%
NUMERICAL SCORE		43	42	47	40	42	41	27	37	35	35	35	43	
TOTAL SCORE		55	51	51	51	50	50	47	48	50	50	50	51	
PERCENTAGE SCORE PER PAPER		78.2%	82.4%	92.2%	78.4%	84.0%	82.0%	57.4%	77.1%	70.0%	70.0%	70.0%	84.3%	

Figure 3 **Findings from the quality assessment tool for the 12 studies included in this systematic review.**

assumptions can only be understood and analyzed through more studies. The methodology of a systematic analysis as used in this review allows those designing PN AA formulations to modify their choice of target plasma arginine values, which is an advantage of this approach.

A limitation of this review is the limited number of studies on this topic. This is mainly due to a lack of monitoring and reporting of plasma AA concentrations in PN-dependent neonate studies because this is not a mandatory monitoring parameter. Another limitation is that studies included in the review included babies with gestational ages ranging from 23 weeks to 32 weeks. It is believed that babies with gestational ages of 30 weeks and above tend to have more developed metabolic and intestinal systems and thus possibly higher arginine concentrations. However, the wide range of gestation durations was accepted in this review because of the limited number of articles otherwise. Furthermore, arginine has not been as much a focus in PN as compared with other AAs, such as glutamine, cysteine, tyrosine, methionine, phenylalanine, and leucine, and thus there are limited data to work with. Besides that, it is well recognized that plasma AA concentrations are not the gold-standard monitoring parameter for assessing optimal AA intake due to various complex reasons such as effects of metabolism, protein turnover, and amino acid in tissues or organs on the plasma concentrations.[57,58] However, the linear relationships as seen in the dose–concentration graphs suggest that plasma concentrations may be a clinically useful indicator of adequate intake.

CONCLUSION

The systematic review yielded 3 important findings. First, it showed that there is an important correlation between the intake and the plasma concentrations of arginine. Given the deficiency of arginine in many contemporary PN formulations, this relationship justifies the need for a study of formulation design to alter the arginine concentration in neonatal PN solution. The percentage content of arginine was a better predictor of plasma arginine concentrations than absolute arginine intake. Second, none of the study design features studied appeared to notably affect plasma arginine concentrations. The review did not suggest a specific dose of parenteral arginine intake to achieve target plasma arginine concentrations, but findings did show that higher contents are needed with current protein intakes to increase the plasma arginine concentrations. Third, the review provided equations that can predict plasma arginine concentrations based on proportion arginine content (%) and absolute arginine intake [mg/(kg × d)].

The dose–concentration graph data suggest that higher protein intake leads to more effective utilization of the additional arginine, and therefore a higher arginine content with high protein intake is needed to bring the plasma arginine concentrations up while ensuring effective use of the extra arginine.

This findings of this review indicate there is a need for well-designed laboratory studies to develop AA solutions that have increased amounts of arginine to meet the requirements of VPNs. Thereafter, clinical trials to investigate the effect of such increased amounts of arginine in AA solutions on the plasma concentrations of neonates need to be conducted to improve the provision of nutrients to PN-dependent VPNs because the proper balance of AAs is crucial for the growth and neurodevelopmental function of the newborn. The 1 study that has shown benefit from arginine supplementation achieved plasma concentrations of 160 micromoles/L. Therefore, it is worth asking the question: if such plasma concentrations are to be achieved with current protein intakes of 3.5–4 g/kg per day, are AA solutions with arginine content of 17%–20% needed?

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Author contributions. C.M.P. conceived the review concept, designed the protocol, performed the literature search, coordinated data selection, data extraction, data analysis, data interpretation, and drafted the initial manuscript. C.M. was involved in conceiving the review, protocol design, data selection, data analysis, data interpretation, and commenting on the manuscript. M.T. was involved in protocol design, data selection, data analysis, data interpretation, and commenting on the manuscript. All authors approved the final manuscript as submitted.

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Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA checklist**

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