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Review article

# Parenteral nutrition for preterm infants: Issues and strategy

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ABSTRACT

Due to transient gut immaturity, most very preterm infants receive parenteral nutrition (PN) in the first few weeks of life. Yet providing enough protein and energy to sustain optimal growth in such infants remains a challenge. Extrauterine growth restriction is frequently observed in very preterm infants at the time of discharge from hospital, and has been found to be associated with later impaired neurodevelopment. A few recent randomized trials suggest that intensified PN can improve early growth; whether or not such early PN improves long-term neurological outcome is still unclear. Several other questions regarding what is optimal PN for very preterm infants remain unanswered. Amino acid mixtures designed for infants contain large amounts of branched-chain amino acids and taurine, but there is no consensus on the need for some nonessential amino acids such as glutamine, arginine, and cysteine. Whether excess growth in the first few weeks of life, at a time when very preterm infants receive PN, has an imprinting effect, increasing the risk of metabolic or vascular disease at adulthood continues to be debated. Even though uncertainty remains regarding the long-term effect of early PN, it appears reasonable to propose intensified initial PN. The aim of the current position paper is to review the evidence supporting such a strategy with regards to the early phase of nutrition, which is mainly covered by parenteral nutrition. More randomized trials are, however, needed to further support this type of approach and to demonstrate that this strategy improves short- and long-term outcome.


## 1. What is at stake?

The incidence of preterm birth is on the rise: 7% of live births in France [1] and 11% worldwide [2] occur before the 37$^{th}$ week of gestation. Very preterm infants are defined by birth before the 32$^{nd}$ week, extremely preterm infants by birth before the 28$^{th}$ week. Using birth weight instead of prematurity for defining nutritional strategies is likely inadequate since three different trajectories can result in low birth weight (LBW): (a) growth deceleration in utero (intrauterine growth restriction, IUGR), (b) steady growth in utero below normal range, or (c) preterm birth with a weight appropriate for gestational age (AGA). The term "small for gestational age" (SGA) refers to the first two settings [3], and it should be borne in mind that preterm infants can be born SGA as well. This paper only addresses parenteral nutrition (PN) in preterm infants *stricto sensu*

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since PN is rarely indicated in low-birth-weight infants born full term and since nutritional requirements and metabolism differ between preterm and LBW term infants.

### 1.1. Preterm nutrition, a challenge for neonatologists

Thanks to progress in neonatal intensive care, more than 90% of very preterm infants survive the neonatal period [4], so that nutrition has become a key determinant for their future health outcome. In utero, bathed in a nearly sterile, isothermal, and oxygen-poor milieu, the fetus receives continuous intravenous feeding through the umbilical vein. Expelled at birth from this cocoon, the premature infant confronts a cold environment that is high in bacteria and oxygen. Its nutritional supply is cut off, its nutrient stores scarce, and its needs are tremendous if this infant is to triple its weight in 3 months as a normal fetus does over the third trimester of gestation.

Due to gut immaturity during the first postnatal week(s), feeding through the gastrointestinal route is at first insufficient to cover such needs: intravenous nutrition (PN) is required during the first few weeks. Despite a more rapid daily increase of feeds, full enteral feeding was only achieved around the 22$^{nd}$ day of life in a cohort of preterm infants weighing less than 1000 g [5]. PN takes over from the maternal–fetal nutrient supply delivered via the placenta, but is far from approaching the complex composition of umbilical blood (e.g., regarding lactate, growth factors, etc.) and should not necessarily mimic the fetal supply of nutrients in view of the dramatic changes in metabolism occurring after birth. PN may result in severe complications (e.g., sepsis, cholestasis, thrombosis) and often falls short of covering needs. Lack of fine tuning of the parenteral nutrient supply, combined with failure or delay to provide adequate enteral nutrition often result in extrauterine growth restriction (EUGR). Despite improvement in nutritional care, EUGR remains common in premature infants. For example, it was observed in 75% of very preterm infants in the early 2000s [6], and still concerns half of the very preterm infants in the most recent studies [7,8]. EUGR may be, at least partly, preventable in infants devoid of severe morbidities such as severe necrotizing enterocolitis, by optimizing PN from birth onwards [9–13]. Moreover, suboptimal nutrition in the first few weeks of life was shown to be associated with a higher risk of nosocomial infection, necrotizing enterocolitis, and hospital admission [14].

### 1.2. Premature birth and the risk of suboptimal growth and neurodevelopment

Premature birth is a well-known risk factor for suboptimal neurodevelopment. At 8 years of age in the EPIPAGE 1 cohort, 77% of infants born very preterm attended a classroom corresponding to their postnatal age, 5% were in special classes, and 18% had repeated a class (vs. 95, 1, and 5%, respectively, for children born full term) [15]. In a landmark study, Ehrenkranz et al. showed that neurodevelopment correlates with the initial growth rate: 600 very preterm infants weighing between 500 and 1000 g at birth were ranked in four growth rate quartiles during the hospital stay. Infants in the 1$^{st}$ quartile gained an average of 12 g/kg/day vs. 21 g/kg/day for those in the 4$^{th}$ quartile. At 18–22 months of age, the prevalence of cerebral palsy was 21% in children in the 1$^{st}$ quartile vs. 6% in the 4$^{th}$ quartile [14]. This difference persisted after adjusting for confounding variables affecting neurological outcome.

Many studies confirmed this observation. In the EPIPAGE 1 study, deficient postnatal growth was found to be associated with poor neurologic outcome for both AGA and SGA preterm infants. Specifically, risk of cerebral palsy was greater for those born AGA and who lost more than 1 SD between birth and 6 months of age compared to those who grew adequately (aOR 2.26 [95% CI, 1.37–3.72]) [16]. Interestingly, regardless of the postnatal growth trajectory, SGA infants showed more frequent behavioral problems and cognitive deficit at 5 years of age. The association of slow growth in the first few weeks of life with poor neurodevelopment is more pronounced in boys. In a cohort of 1221 boys and 1056 girls born preterm, the odds ratio for suboptimal neurodevelopment at 2 years of age was 3.2 for boys who experienced EUGR vs. those who did not, and the risk was 1.8 (95% CI, 0.7–4.2) and 0.95 (95% CI, 0.4–1.9), respectively, in girls [17]. Most studies in the field, however, are observational. As such, they cannot prove a causal relationship: premature infants who grew slowly most likely were frailer or more severely ill, which could have led to the prescription of less optimal nutrition during their hospital stay.

### 1.3. Nutritional imprinting

The concept of nutritional imprinting emerged in the 1990s when David Barker showed that infants born with a low birth weight are exposed to a higher risk of developing obesity, type 2 diabetes, hypertension, high cholesterol, and coronary disease in adulthood [18,19]. The first cohorts included children born SGA in the 1900s, who were mostly term infants. More recent work shows that adults born preterm are exposed to increased risk of hypertension and insulin resistance in the long run [20–22]. In a meta-analysis of 27 studies, collecting more than 17,000 adults born preterm, LDL cholesterol and blood pressure were 0.14 mmol/L (95% CI, 0.05–0.21) and 4.2 mmHg (95% CI, 2.8–5.7) higher for LDL and blood pressure, respectively, in adults born preterm than in those born full term [23]. Such differences, albeit small, are associated with increased cardiovascular risk on a population scale. In contrast, no significant difference was observed regarding corpulence, blood glucose, or fasting serum insulin [23] nor insulin resistance [24].

Whether or not early markers of risk of hypertension and insulin resistance can be found during childhood remains a matter of debate. In a British cohort of 209 adults born preterm, the growth rate in the upper quartile during the first 2 weeks of life was associated with reduced flow-mediated arterial dilation at adulthood [25]. In a French cohort, preterm birth was associated with elevation of systolic blood pressure and arterial stiffness (assessed by pulse wave velocity) at adulthood [26], but in another study conducted earlier at 6 years of age, no such association was found [27]. Factors other than nutrition obviously play a role as well. Preterm babies undergo significant stress and stress-related hormones may also play a major role in these outcomes.

### 1.4. Risk of disease at adulthood due to rapid catch-up growth

Several studies suggested a deleterious effect of excess growth in infancy or childhood in preterm infants. In the study by Regan et al., weight gain between 0 and 4 years was associated with increased insulin resistance assessed at 10 years of age [28]. In a more recent study, growth of preterm infants in early infancy did not impact metabolic status in adolescence, in contrast to rapid weight gain in childhood [29]. The most dangerous weight gain may in fact be that occurring after 1 year of age. A recent review showed that growth between birth and 12–18 months post-term has no significant effect on later blood pressure and metabolic syndrome in adulthood. In contrast, growth during late infancy and childhood appears to be a major determinant of later metabolic and cardiovascular well-being [29].

### 1.5. Impact of nutrition on body composition

Fetal weight triples over the 3$^{rd}$ trimester, with a weight gain around 15 g/kg/day, consisting of ≈1.5–2.0 g/kg/day of fat,

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