REVIEW ARTICLE

Feeding growth restricted premature neonates: a challenging perspective

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ABSTRACT

Nutrition in the postnatal period is essential to achieve optimal growth and maintain biochemical normality. Feeding growth-restricted premature neonates remains a big challenge for pediatricians and neonatologists. The choice of milk is one of the biggest challenges. Breast milk is recommended, although feeding with preterm formulas can ensure a more consistent delivery of optimal levels of nutrients. The timing of introduction of feeds and the rate of advancement of those feeds in preterm infants are both topics of significant controversy. Early feeding is advantageous because it improves the functional adaptation of the gastrointestinal tract and reduces the duration of total parenteral nutrition. A faster rate of advancement will also reduce the duration of need for parenteral nutrition. Despite this, enteral feeding is often delayed and is often slowly increased in high-risk infants because of a possible increased risk of necrotizing enterocolitis (NEC). Growth-restricted neonates are at increased risk of developing NEC due to a combination of antenatal and postnatal disturbances in gut perfusion. If enteral feeding is introduced earlier and advanced more quickly, this may lead to increased risk of NEC, but slower feeds extend the duration of parenteral nutrition and its risks and may have adverse consequences for survival, growth, and development. Premature infants pose a significant nutritional challenge. Overall, we would suggest the preferential use of human breast milk, early minimal enteral feeds, and standardized feeding protocols with cautious advancements of feeds to facilitate gastrointestinal adaptation and reduce the risk of NEC, however further research is needed.

KEYWORDS:

Premature neonates; Small for gestational age; Growth restriction; Nutrition; Necrotizing enterocolitis; Breast milk; Total parenteral nutrition.

INTRODUCTION

Advances in neonatal medicine over the past few decades have led to improvements in survival of extremely premature neonates worldwide. However, short-term and long-term morbidities such as neurodevelopmental, respiratory, renal, and cardiovascular problems are known to occur in the surviving children. Optimal care in the neonatal period is crucial and this care includes balancing the risks of adequate early nutrition and its possible complications. Studies have demonstrated that sub-optimal nutrition during

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Received: 29 March 2018 | **Accepted:** 20 November 2018

How to cite this article:
Paul SP, Kirkham EN, Hawton KA, Mannix PA. Feeding growth restricted premature neonates: a challenging perspective. Sudan J Paediatr. 2018;18(2):5–14.
https://doi.org/10.24911/SJP.106-1519511375

the early neonatal period can have long-term health consequences [1].

The mature gut in a term neonate is a complex organ; there are villi increasing the surface area for absorption, specialized cells to produce enzymes and hormones and it has its own immune system. In premature babies, although structurally formed, the gut behaves more functionally immature with decreasing gestational age. Coupled with their immature immune system, this poses difficulties to the clinicians deciding how to feed these babies [2]. The problem is further compounded in intra-uterine growth restricted (IUGR) premature neonates born with a reduced, absent or reversed end-diastolic flow detected on antenatal ultrasound scans.

This review article discusses the available relevant literature and includes systematic reviews, randomized controlled trials, cohort and case-control studies. The comprehensive overview on the available evidence provided in this article should be helpful for pediatricians and neonatologists managing nutrition of growth restricted premature neonates.

WHY GROWTH RESTRICTED PREMATURE NEONATES ARE AT RISK?

IUGR is defined as the diminished growth velocity documented by at least two intra-uterine growth assessments. Small for gestational age (SGA) describes newborns whose weight or length at birth is at least two standard deviations below the mean for gestational age. This means that not all babies who measure as SGA are IUGR but simply measure small constitutionally. Regular monitoring of fetal growth by Doppler ultrasound scan is commonly done in pregnant ladies where intrauterine growth restriction is suspected/detected. In the IUGR fetus, hypoxemia produces preferential circulatory redistribution of blood toward the brain, thus compromising supply to the viscera and placenta, resulting in absent or reversed end-diastolic flow velocities (AREDF) in the umbilical artery or aorta [3]. Fetal hypoxic-ischemic injury of the intestines may occur even before birth due to a combination of fetal hypoxia and increased mesenteric vascular resistance which preferentially redistributes blood to the brain and adrenal gland [4].

Nutrient supply through the placenta is compromised in IUGR fetuses, leading to growth restriction. As such, this group of babies may, therefore, be deemed to require a higher energy supply than premature babies born otherwise without any growth restriction [5]. However, in the postnatal period, due to the compromised blood supply, the intestines are more susceptible to stasis, abnormal colonization, bacterial invasion, and pseudo-obstruction [3,6]. Combinations of antenatal and postnatal disturbances in gut perfusion put these IUGR infants at higher risk of feed intolerance and developing necrotizing enterocolitis (NEC), thereby posing significant challenges in establishing enteral feeds. NEC is an acute inflammatory condition of the bowel, characterized by ischemic necrosis which may lead to perforation and destruction of the gut. It is well recognized that susceptibility for developing NEC correlates inversely with gestational age.

CHALLENGES OF FEEDING GROWTH RESTRICTED PREMATURE BABIES

Feeding growth-restricted premature neonates remains a challenge for pediatricians and neonatologists. The baby who is born premature misses out on the intrauterine time of rapid fetal growth and nutrient accumulation. Nutrition in the postnatal period is therefore essential to achieve optimal growth, maintain biochemical normality, avoiding toxicity, and/or side effects from parental nutrition. All these factors are likely to be achieved by establishing full enteral feeding early [2]. There are two methods of feeding preterm babies: enteral or parenteral nutrition. Table 1 highlights the advantages and disadvantages of the two methods of providing nutrition to neonates [2,7–9].

A systematic review compared premature babies with and without AREDF [3]. It included 14 studies with 659 premature neonates with AREDF and 1,178 without AREDF. The review reported significantly increased risk of NEC in the AREDF

Table 1 - Advantages and disadvantages of nutritional methods.

Parenteral nutrition	Enteral nutrition
Advantages:	Advantages:
– Early calorie intake – Prevents catabolism – Delivery of optimal nutrition – Reduced risk of NEC	– Promotes growth and development of gut – Stimulates hormone secretion, motility, and microbial colonization – Reduced feed intolerance – Reduced risk of infection – Avoids muscle atrophy – Shorter hospital stays – Earlier full enteral feeding established
Disadvantages:	Disadvantages:
– Risks of starving the gut—thinning of the mucosa, reduction in cell growth and division, shortening of villi, and impairment of enzyme production – Growth restriction – Expensive – Infection risk, e.g., percutaneously inserted long line-related sepsis – Cholestasis – Other complications including cardiac tamponade, osteopenia of prematurity, drug-administration errors, metabolic disturbance	– Risk of NEC – Need for careful monitoring to ensure optimal nutrition is being delivered, especially if maternal expressed breast milk supply is limited or not available

group (OR 2.13) [3]. Similar findings were reported in another review with 29,916 premature neonates, growth restriction was more likely to be associated with NEC, increased mortality, need for respiratory support at 28 days of life, and retinopathy of prematurity [10].

Advances in antenatal and neonatal practices have improved survival rates and long-term outcomes for very preterm infants, although the incidence of NEC and late-onset infection still remains high [9]. Modifiable risk factors related to enteral feeding that may improve outcomes include the timing of introduction of feeds, duration of trophic feeding, the rate of advancement of feeds, and the type of milk used [11]. There is, however, a lack of consensus regarding how best to feed small, preterm IUGR infants. Early introduction and rapid achievement of full enteral feeding remain a priority in the nutritional management of preterm infants as it reduces the need for parental nutrition (PN) with its associated risk of infection and increased the length of hospital stay. However, the need to attain enteral feeds rapidly is often difficult due to the physiological immaturity of the gut and compromised gut perfusion in IUGR neonates [1].

EPIDEMIOLOGY

The occurrence of AREDF has been associated with poor fetal outcome and occurs in about 6% of high risk pregnancies [2]. NEC is the most common neonatal gastrointestinal emergency, with 85% of cases being seen in those born either <32 weeks gestation or with a birth weight <1.5 kg. This is attributed to immature barrier function, poor digestion of feeds, and immature immune system of these infants [12]. The incidence of NEC varies depending on ethnicity; for example, it is higher in black male infants, where approximately 12% of infants born <1.5 kg are likely to develop NEC [13]. Infants who develop NEC experience more nosocomial infections, have lower nutrient intake, grow more slowly, and have a longer duration of neonatal intensive care and hospital stay than those without NEC. Post-NEC infants

are at an increased risk of neurological disability [9, 14] leading to a huge financial burden to the healthcare system [11].

THE DEBATE CONTINUES—WHAT MILK FEED IS BEST?

Maternal breast milk is considered the best form of enteral nutrition as in addition to catering for a balanced nutrition, it contains immunoglobulin that promotes intestinal adaptation and maturation, improves feed tolerance, and provides protection against infection and inflammatory disorders [14]. However, feeding with standard preterm formulas can ensure a more consistent delivery of optimal levels of nutrients as human milk nutritional contents may vary both with maternal breast milk supply and the stage of lactation it is collected in [14]. There is often this debate whether the nutritional requirements of preterm infants, especially those with inadequate stores who often get subjected to additional metabolic stresses, will be entirely met by breast milk.

A large prospective randomized trial of early diet carried out in the 1980s by Lucas and Cole demonstrated that breast milk provided a protective effect for developing NEC (OR 10.6 for confirmed cases) [15]. The findings of this research have been supported by later studies. A Cochrane review found that preterm babies fed on formula milk were twice more likely to develop NEC as compared to those fed on breast milk (despite a slower weight gain) [14]. A recent trial involving 207 premature infants with a birth weight 500–1,250 g randomized to receive human or formula milk found markedly lower rates of NEC in the human milk group and the number needed to treat to prevent one case of NEC was 10 [16]. Short- and long-term benefits of being fed on breast milk are well known, e.g., improved feed tolerance and neurodevelopmental outcomes, reduced infection rates, hospital readmissions during childhood, and rates of developing NEC [12].

Given that maternal breast milk often does not meet the nutritional requirements of preterm babies, supplementing breast milk with fortifier to add extra carbohydrate, protein, calcium, and phosphorus improves weight gain and growth [12]. There are, however, concerns that it may increase the risk of NEC. No statistically significant increase in NEC incidences were described in a Cochrane review for infants receiving fortified breast milk [17], and it is an established practice to fortify breast milk with cow's milk-based fortifiers in neonatal nutrition [12].

The anti-infective property of mother's breast milk is considered to be of significant benefit and, therefore, slightly slow short-term growth, particularly in low- or middle-income countries far outweighs the issue of growth potential with breast milk. In India, a randomized trial in low birth weight (LBW) infants found that serious infections were less common in infants allocated to receive expressed human milk in comparison to formula milk [18, 19].

CURRENT CHALLENGES AND EVIDENCE

Initiation of feeds

It remains a topic of significant controversy as to when may be the appropriate time to start enteral feeds in preterm infants. Introduction of enteral feeds early is beneficial as it improves the functional adaptation of the gastrointestinal tract and reduces the duration of total parenteral nutrition (TPN) and its complications (Table 1). TPN is considered as an alternative method of providing balanced nutrition comprising of carbohydrate, amino acids, and lipids; side effects, however, are common and the available evidence suggests that delaying feeds and using TPN for a long period could be detrimental [3]. Early feeding can also result in shorter duration of hospital stays and establishing of full enteral feeding earlier [7]. Due to the possible increased risk of NEC in premature IUGR babies, the introduction of enteral feeding is often delayed in most centers and it is not uncommon to see associated complications due to prolonged TPN use [4].

A recent Cochrane review with 10 randomized controlled trials (RCTs) involving 3,573 babies found no detrimental effect of slowly increasing the volume of enteral feeds at 15–20 ml/kg/day compared with fast increase at 30–40 ml/kg/day

[20]. On the contrary, advancing the volume of enteral feeds at a slower rate will lead to delay in establishing full enteral feeds by several days and may increase the risk of invasive bacterial infections and TPN-related complications [20].

Feeding IUGR babies is a further challenge as they are already undernourished at birth and good nutrition and growth are essential but they are also at higher risk of developing NEC; hence, the introduction of enteral feed, therefore, often gets delayed [21]. These babies often have poor tolerance of enteral feeding, and there exists anxiety amongst parents and health professionals about developing NEC compounding the problem in establishing full enteral feeds. Two surveys from the United Kingdom (UK) revealed considerable variation in practice between neonatal units [22]. In the Southwest of England, enteral feeding was delayed in 9/12 hospitals for IUGR babies under 32 weeks gestation. Abnormal Doppler's, polycythemia, the presence of umbilical artery catheter and absence of breast milk were highlighted as reasons for the delay in advancing feeds. While in 15 hospitals in the East of England, 5 units commenced feeds on day 1, 2 delayed until day 7, with the remainder introducing feeds between day 2 and day 5. The main reason cited for the delay was to prevent NEC [22].

The Abnormal Doppler Enteral Prescription Trial (ADEPT) study from the UK was undertaken to understand whether early enteral feeding or late enteral feeding of IUGR babies born with abnormal Doppler findings of umbilical artery was more beneficial. Results from ADEPT revealed no difference in the incidence of NEC or late-onset sepsis and the early feeding group achieved full feeds much earlier (by 3 days) with less dependence on parenteral nutrition (PN), shorter duration of hospitalization, and a lower incidence of cholestatic jaundice [8, 23]. This is the largest interventional study in this patient population and is consistent with other concurrent research [7, 24] suggesting no clear benefit of delaying feeds [23]. However, in the ADEPT study, subsequent subgroup analysis of the babies of <29 weeks suggested that successful advancements of feeds might be slower in this vulnerable population, and clinicians should, therefore, exercise patience when feeding this group of infants as their NEC risk is very high [25].

Delayed introduction of enteral feeds in centers where there is an established provision of adjunctive PN, may confer a less nutritional disadvantage to premature IUGR babies. However, in settings of technologically less-developed healthcare provision in resource-limited countries, where PN is not easily available and severe infections remain a more important cause of neonatal mortality and morbidity, the nutritional and immunological advantage establishing of early enteral feeding with maternal breast milk may actually prove beneficial [18, 19, 21, 26].

Minimal enteral feeds

Minimal enteral feed (MEF), also referred to as gut-priming or trophic feeding is an alternative approach followed in some centers and is aimed to improve feed tolerance and prevent complications of prolonged PN. It is defined as small volumes of feeds of 12–24 ml/kg/day continued for a period of time before advancing the feed volumes. Enteral fasting during the early neonatal period has potential disadvantages because gastrointestinal hormone secretion and motility are improved by enteral feeds. Early trophic feeding, therefore, accelerates gastrointestinal physiological, endocrine and metabolic maturity, gut motility and blood flow, and promotion of colonization by commensal bacteria allowing infants to transition to full enteral feeding more quickly [9, 27].

A recently updated Cochrane review included nine trials comparing MEF to no enteral feeds in 754 neonates. No statistically significant differences were found between the two groups in time to reach full feeds, length of hospital stay, rates of NEC, feed tolerance, or growth rates [28]. Further large-scale studies with adequate sample sizes are needed to establish the safety of the MEF approach [3]. However, uncertainty remains about the effect of MEF on SGA infants as most trials have previously excluded these infants. A randomized pilot trial looking at MEF use in preterm infants with IUGR and abnormal Doppler's found no significant effect on the incidence of NEC or feeding intolerance [29]. The findings from this Greek study and evidence

available from previous studies do not support a delay in feeding, although further research is needed to establish the safety profile [29].

To summarize, for extremely preterm babies, there is no good evidence to support delaying feeds excessively. A period of MEF appears to be safe and beneficial with the earlier establishment of feeds, reduced length of stay and reduced use of PN but optimal duration needed to establish full enteral feeds remains unclear.

Rate of feed advancement

There is a lack of clear and robust evidence regarding the rate of advancement of enteral feeding in IUGR premature babies. It is considered that if enteral feeding gets introduced early and advanced fast, higher risk of developing NEC remains possible. Increasing the speed of enteral feeds at a slow rate delays the establishment of full enteral nutrition, extends the duration of PN and its risks and can have less favorable outcomes in infant's survival, growth, and development [4, 20].

A recent Cochrane review of 3,573 vulnerable infants found no difference on feed tolerance in either arm of speed of increasing feeds—slow (15–20 ml/kg/day) versus faster rates (30–40 ml/kg/day), neither found significant difference in the risk of developing NEC [20]. The clinical importance of this observation remains unclear as long-term outcomes were not assessed in the studies included in the analysis [20]. In current clinical practice, a conservative approach to increasing enteral feeding is taken; there are consequences of such an approach that needs to be considered [20]. The rate of feed advancement should be guided by clinical judgment, including assessing the abdomen, for distension or tenderness, and the passage of stools. A large multicentre UK-based speed of increasing milk feeds tial (SIFT) has recruited neonates to evaluate the effect of two speeds of daily increments of milk feeds in very preterm and LBW infants [30]. Preliminary results from the SIFT trial regarding their primary outcomes showed that fast feeding (30 ml/kg/day) was not detrimental in comparison with slow feeding (18 ml/kg/day) in terms of feeding issues [31].

Clinicians need to be careful about recommending a universal approach of the rapidly increasing speed of enteral feeds in all LBW babies. Infants weighing <1,000 g who are moderately unwell with hemodynamic instability may not be appropriate candidates for rapid enteral feeding protocols and cautiously increasing feeds at a slower rate may need to be considered [32].

In the context of developing nations, the use of early and rapid enteral feeding protocols using exclusive human breast milk is likely to decrease hospital-related morbidity, less infective episodes, and may actually lead to better weight gains [33].

Mode of feeding

There are currently no studies available which exclusively looked at SGA neonates and the best mode of feeding them. Infants <32 weeks are not able to co-ordinate suck, swallow, and breathe at the same time. A Cochrane review of seven trials comparing continuous versus intermittent milk feeding methods did not find a difference in time to establishing full enteral feeding, feed intolerance, growth, and incidence of developing NEC [34]. There are advantages to both approaches. Continuous feeding may reduce energy expenditure and improve feed intolerance, nutrient absorption, and growth, whereas intermittent bolus method will be more physiological, promoting the cyclical pattern of gut hormone release important for the development of the functioning of the gastrointestinal tract. Slow bolus feeds may be preferable in most cases as compared to continuous feeds, but this strategy lacks a clear evidence base and remains debatable [35].

Standardized feeding

The implementation of standardized feeding regimens is likely to decrease the rates of developing NEC. The advantage of such guidelines lies in the fact that it provides intense nutritional support through a combination of early PN and starting early enteral nutrition followed by a progressive reduction in PN as enteral feed volumes get increased gradually [36]. A meta-analysis which included six observational studies found significantly decreased incidence of NEC rates as a common theme when vulnerable neonates were fed through a standardized feeding

regime, irrespective of the finer details of each protocol [37]. It is important that every neonatal unit looking after these babies implement a standardized feeding regimen based on the current best evidence for their vulnerable patient groups at higher risk of developing NEC.

Other problems

There are other recognized associations of prematurity which are known to affect the blood flow to the gastrointestinal tract. The presence of a patent ductus arteriosus (PDA) can reduce diastolic blood flow in the descending aorta and mesenteric vessels, while treatment with indomethacin or ibuprofen to close the PDA causes vasoconstriction. Dopamine, an inotrope used for blood pressure management, is known to cause vasoconstriction and early use of steroids in very LBW infants increases the risk of gut perforation [38]. There are lack of good quality RCTs in the above situations about whether to withhold feeds while treating with these drugs or if it will be safe to continue with smaller volume enteral feeds; the decision, therefore, has to rest on the judgment of the clinical teams.

THE WAY FORWARD— THE AUTHORS' OPINION

Evidence available at present suggest that introducing progressive enteral feeding before 4 days after birth and advancing the rate of feed volumes at >20 ml/kg/day does not appear to increase the risk of NEC [20]. These findings are consistent with current policy and practice followed in Scandinavian countries. Delayed introduction or slow advancement of enteral feeds results in several days of delay in the time taken to establish full feeds and, in turn, regaining of birth weight; the long-term clinical importance of these effects is unclear [9].

Using the currently available strategies for establishing enteral nutrition for extremely preterm IUGR neonates, optimizing growth can be difficult as is evident from an Australian study where 38/220 were IUGR at birth. Incidence of postnatal growth restriction was significantly higher in IUGR group (73%) versus 45% in non-IUGR neonates (p = 0.003) [39]. There is a lack of robust data in this selective population, further RCTs are needed to fully establish what feed is the best, when to start it, and how quickly it is safe to advance it. Given the currently available information, it seems that the best strategy is to feed these vulnerable babies with maternal breast milk where possible, to encourage MEF with cautious early feed advancements based on a standardized feeding protocol within the hospital [40], or for a region considering, there will be movement of these babies depending on the level of neonatal care they need. Many units preferring to use breast milk will use donor expressed breast milk in the absence of maternal milk owing to the well-recognized risk of NEC in formula-fed babies [14]. The ultimate aim about the approach should be to improve weight gain and decrease the time to establish full feeds and not adversely heighten the risk of developing NEC. The literature review suggests a projected growth velocity rates of approximately 15 g/kg/day for weight, ≃1 cm/week for length and 0.5–1 cm/week for head circumference for preterm infants while in the neonatal units [41]. Although anecdotal, we use 20–30 g/day as our target for weight gain in our centers.

A recent Cochrane review has found low-quality evidence that lactoferrin supplementation to enteral feeds with or without probiotics decreases late-onset sepsis and NEC stage II or III in preterm infants without adverse effects [42]. Results from trials such as the UK-based SIFT, enteral lactoferrin in neonates (ELFIN), and mechanisms affecting the gut of preterm infants in enteral feeding trials (MAGPIE) studies are awaited or have started becoming available and these data will hopefully shed further light on the issue [43].

The current research is also looking at the use of probiotics supplement to improve colonization of the preterm gut with commensal flora which may have a beneficial role in reducing the incidence of NEC [12]. A Cochrane review showed beneficial evidence of probiotics in reducing the incidence of NEC and mortality in the probiotic group [44]. A meta-analysis with 19 RCTs (n = 4,527 neonates) found that in the probiotic group time to establishing full enteral feeds was shorter, although the safety and efficacy have not been fully evaluated [13]. A multicentre trial is

currently underway to evaluate the effect and safety of probiotics in this patient group. Research is also looking into genetic predisposition to NEC, therapeutic hypothermia (well-established treatment for hypoxic-ischemic brain injury) [45] and stem cell therapy.

CONCLUSION

The growth-restricted premature infants pose a significant nutritional challenge to manage and need a delicate balance for establishing early enteral feeds without increasing the risk of NEC. Enteral feeding is safest from an infection perspective, but immature gut physiology puts these babies at higher risk of developing NEC. Abnormalities of splanchnic blood flow persist during the first week of life, providing physiological justification for a delayed and careful introduction of enteral feeding but such an approach predisposes premature IUGR babies to the risks associated with PN with no trials to date showing any benefit of the delayed establishment of enteral nutrition. MEF based on current evidence appears to be safe, but there is a lack of evidence on which to base other strategies of feeding. Few trials are currently in progress, the results of which may provide further direction to some of the issues discussed in the article. More multicenter RCTS are required to provide guidance on the unanswered questions. Currently, preferential use of human breast milk, early commencement of MEF and standardized feeding protocols with cautious advancements of feeds are practiced in most centers to facilitate gastrointestinal adaptation, improve feed tolerance, and reduce the risk of NEC.

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