

Chapter 2

Minimal Enteral Feeding

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Abstract In preterm infants, enteral feeding is often delayed by hours to days after birth for fear of feeding intolerance due to immaturity, to avoid the accentuation of hypoxic/ischemic intestinal injury that might have been sustained *in utero* due to maternal risk factors such as pre-eclampsia, placental insufficiency, or chorioamnionitis, or after birth due to the presence of cardio respiratory compromise in the early neonatal period, and as a protective strategy to reduce the risk of necrotizing enterocolitis. However, some degree of luminal nutrient exposure is essential to prevent intestinal mucosal atrophy. Minimal enteral feeding is a clinical compromise where small volumes of maternal milk or formula, typically 12–24 mL/kg/day, are provided to avoid complete enteral fasting for prolonged periods. Although preclinical and observational human studies indicate that minimal enteral feeding is likely to be beneficial through maturation of gut motility, induction of gut hormones, and prevention of adverse effects of enteral fasting and parenteral nutrition on the mucosa, randomized clinical trials conducted thus far have not provided conclusive evidence to confirm these benefits. Current clinical evidence suggests that minimal enteral feeding is relatively safe and does not increase incidence of NEC. However, the amount, duration, and the rate of advancement of minimal enteral feeding remain controversial. There is a need for a large, multi-centric study with pre-defined statistical and clinical definitions to draw strong conclusions. In this chapter, we review the physiological rationale and appraise the quality of existing evidence to support minimal enteral feeding in the neonatal intensive care unit.

Key points

- Minimal Enteral Feeding is a way to provide luminal nutrient stimulation to the immature or vulnerable neonatal gastrointestinal tract to prevent the adverse effects of prolonged enteral fasting

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- Evidence from animal and human studies strongly suggests that minimal enteral feeding can be beneficial by promoting physiologic gut function, maturation of gut motility, induction of gut hormones, and prevention of adverse effects of enteral fasting and TPN dependence on the mucosa
- Evidence strongly suggests that minimal enteral feeding is relatively safe, and does not increase incidence of NEC
- Amount, duration, and speed of advancement of minimal enteral feeding remains controversial
- There is a need for well-designed research with pre-set statistical and clinical measures to draw strong conclusions with minimal heterogeneity

1 Introduction

The introduction of enteral feedings is often delayed in very low birth weight (VLBW) infants due to the fear of poor tolerance in the presence of multi-system dysfunction, immaturity of the gastrointestinal tract, and the risk of necrotizing enterocolitis (NEC). However, concerns also remain that gut ‘disuse’ during extended periods of enteral fasting could delay or alter the postnatal adaptation of the premature intestine and prolong the need for parenteral nutrition [9, 102]. Minimal enteral feeding is a compromise alternative where small volumes of maternal milk or formula, typically 12–24 mL/kg/day, are provided to avoid complete enteral fasting [30]. Minimal enteral feeding has been described in the literature by various synonyms such as ‘minimal enteral nutrition’, ‘gut priming’ for stimulation of gastrointestinal function, ‘trophic feedings’ for promotion of gut growth, and ‘hypocaloric feedings’ as a reminder that minimal enteral feedings are not intended to be the primary or sole source of nutrient supply.

2 Historical Perspective

Minimal enteral feeding seems to have first appeared in the literature in animal studies in the 1950’s. In the clinical setting, minimal enteral feeds first found favor in adult patients after bowel surgery and were used with an intention to promote tolerance to feeding [16, 35]. Studies in critically-ill and preterm infants started to arise in the 1970’s and 80’s as an intervention to promote gut maturation. The term “minimal enteral nutrition” was first used in the mid 1980’s by Lucas et al. [14], who showed that enteral administration of very small quantities of human milk in term and preterm infants was associated with higher plasma concentrations of gut hormones than in enterally-fasted infants on parenteral nutrition. Cumulative feeding volumes (since birth) as small as 12 mL/kg body weight were associated with increased plasma enteroglucagon, gastrin, and gastric inhibitory peptide, and maximal responses were obtained with an average total intake of 50 mL/kg. Although larger enteral volumes

(still lower than full enteral feeds) were needed to produce a neurotensin or motilin surge, these findings suggested that minimal enteral feeding could help maintain mucosal integrity and possibly promote gut maturation in enterally-fasted infants dependent on parenteral nutrition [14]. In another study at about the same time, Slagle et al. [59] randomized 46 VLBW infants receiving parenteral nutrition to be either enterally-fasted or to receive minimal enteral feeding (12 mL/kg/day) from postnatal day 8 through day 18. After day 18, feedings were increased by 15 mL/kg/day in both groups. The minimal enteral feeding group showed improved tolerance to feedings, manifested by fewer days when feedings were withheld or when gastric residuals totaled more than 10 % of feedings. More infants in the minimal enteral feeding group achieved enteral intakes of 120 kcal/kg/day by 6 weeks than in the delayed feeding group (94 % vs. 64 % infants, respectively; $p < 0.05$). In other early studies, [2, 41] enteral feedings of 12–24 mL formula/kg/day (4–20 kcal/kg/day) during the first 8 days in ill VLBW infants was associated with better weight gain, faster decline in serum bilirubin levels, reduced cholestasis, better tolerance to subsequent larger-volume feedings, and faster attainment of full enteral feeds than infants who were enterally-fasted during the same period [64, 79].

The terms ‘gut priming’, ‘trophic feedings’, and ‘hypocaloric feedings’ became established in the 1990’s as use of minimal enteral feeding was favorably reviewed in the nutritional management of critically-ill preterm neonates [25]. In the last 2 decades, there has been a gradual paradigm shift from avoiding enteral feeds to widespread acceptance of minimal enteral feeding as a preferred mode of initiation of feeding in critically-ill VLBW and extremely low birth weight (ELBW) infants. However, the volume, duration, methods and frequency of feedings vary considerably between individual centers and with limited evidence, there are no clear guidelines for practice.

3 Physiological Considerations in Early Introduction of Enteral Feedings

The developing gastrointestinal tract handles large volumes of amniotic fluid in utero Starting at 8–11 weeks, the fetus ingests increasing amounts of amniotic fluid during mid- and later gestation. In the 3rd trimester, the fetus swallows nearly 550 mL/day (range 210–840 mL/day) of amniotic fluid [80, 81]. Although amniotic fluid is largely comprised of water (nearly 98–99 %), its composition varies with gestation [19]. In the 1st trimester, the osmolality of amniotic fluid is 290 mOsm/kg and is isotonic to maternal serum. However, as the fetal skin becomes keratinized and the renal function matures near term, the osmolality of amniotic fluid falls to 255 mOsm/kg. Despite its low caloric density and nutrient content (protein content ~1 % weight/volume), amniotic fluid is an important source of nutrition for the 3rd trimester fetus who swallows large volumes (up to 20 % of body weight per day) that may provide for up to 10–20 % of the daily energy needs [86].

Adverse effects of enteral feedings, real and presumed Following preterm birth, enteral feedings are withheld for a variety of pre- and postnatal reasons. Feedings are frequently withheld to allow the gastrointestinal tract to recover from actual/presumed ischemic insults that might have occurred *in utero* due to maternal pre-eclampsia, chorioamnionitis, placental insufficiency (indicated by the absence or reversal of umbilical arterial or aortic blood flow on Doppler studies), and fetal infection. Feedings may also be withheld for postnatal issues, if the infant ‘looks unwell’, has respiratory distress, persistent patency of the ductus arteriosus, or has had perinatal hypoxic-ischemia, events that could cause hypoxemia and/or hypotension and thereby trigger the ‘diving’ reflex, redirecting oxygenated blood away from the gut and towards vital organs such as the brain, heart, and adrenal glands. Although some infants with one or more of the above conditions may have truly sustained intestinal ischemia, most infants who receive presumptive treatment do not show any clinical signs of intestinal injury. In the absence of reliable biomarkers of intestinal ischemia, the care-provider is often left with no choice but to presume the worst-case scenario in all ‘at-risk’ infants that the gut mucosa needs time to recover from ischemic injury before enteral feedings can be initiated safely.

Developmental constraints to enteral feeding in the preterm infant Several studies have investigated the ontogeny of intestinal peristalsis and digestive function. Although not quite as well-developed as in the term infant, nutrient absorption in preterm infants is adequate to sustain normal growth [43, 60]. Similarly, with the exception of lactase activity that matures at about 34 weeks gestation, most digestive functions are in place by the end of the 2nd trimester [74]. Gastric acid output, bile synthesis, and exocrine pancreatic function are also considered adequate for digestion [12, 28, 65, 87]. Preterm infants can also increase their splanchnic blood flow after feeds, although the immature autoregulatory mechanisms can become overwhelmed under stress related to hypoxemia, shock, anemia, and transfusions [34, 51, 68].

Immaturity of motor function is a major limitation to successful enteral feeding in preterm infants. Readiness for oral feeding requires suck-swallow coordination, which develops at about 32 weeks gestation [56]. Infants born earlier than 32 weeks are at risk of aspiration of gastric contents into the trachea and lungs during oral feeding. To avoid recurrent overt or micro-aspirations, most clinicians prefer gavage as the modality of choice for VLBW infants.

In the gastrointestinal tract, effective propulsion of nutrients requires anterograde peristaltic contractions that are organized in time and location, and are synchronized with a relaxation response in segments immediately distal to the contraction wave. The motor activity of the gastrointestinal tract is regulated by inputs from the extrinsic nervous system, which includes the parasympathetic and sympathetic systems, and also from the intrinsic nervous system that is comprised of nerves that reside solely in the gastrointestinal tract [103]. Although major neural elements are in place by 15–18 weeks gestation, [96] the motor activity of the gastrointestinal tract continues to show signs of immaturity until late in the 3rd trimester such as laxity of the lower esophageal sphincter, delayed gastric emptying, and slow duodenal-anal transit [7, 97, 103, 109].

Prolonged enteral fasting can cause gut mucosal atrophy The absence of food in the gastrointestinal tract produces mucosal and villous atrophy and decreased expression of enzymes necessary for digestion and substrate absorption [29, 30]. In experimental animals, prolonged fasting can clearly cause small intestinal atrophy, loss of villus height and crypt depth, decreased intestinal weight, and enterocyte apoptosis [26]. The effects of enteral fasting vary with species and are most prominent in rodents, which can lose up to 50 % of the mucosal mass. Loss of mucosal mass is also seen in suckling pigs, but is less striking at about 20 %. In humans, the data are less clear. In critically-ill adults, enteral fasting for as few as 4 days was associated with decreased villus height and with abnormalities in lactulose-mannitol absorption [98]. In other studies, children with inflammatory bowel disease who were dependent on parenteral nutrition for 9–12 months showed relatively modest (about 10 %) mucosal atrophy [1]. The effects of enteral fasting have not been studied in neonates. However, ingestion of both amniotic fluid *in utero* as well as feeding after birth are required for the development of the crypt-villus histoarchitecture, [4, 27, 76, 94] and one can safely infer that the effects of enteral fasting are not likely to be less pronounced in infants than in older children and adult subjects.

Enteral fasting is also associated with decreased gut hormonal responses, including the hormones and trophic peptides produced in the oral cavity, stomach and the intestine in response to enteral feeding [32]. A variety of immune deficits can also develop, such as decreased mucosal IgA, increased expression of adhesion molecules, and leukocyte recruitment, which may increase the risk of mucosal inflammation [4, 32]. Fasting-related mucosal atrophy may also be directly associated with bacterial translocation from the lumen to mesenteric lymph nodes in rodents, although these findings need confirmation in humans [69].

Association between enteral feedings and necrotizing enterocolitis (NEC) Observational studies indicate that more than 90 % cases of NEC occur in infants who have received enteral feedings; many cases have a history of recent volume advancement or re-initiation of enteral feedings after a period of enteral fasting [20, 44]. The association may have an element of biological plausibility because enteral feeding, particularly with formula, could alter splanchnic perfusion and increase the risk of ischemic injury, [108] cause osmotic injury to the mucosa, and in the presence of undigested substrate in the gut lumen, promote bacterial overgrowth [57, 63]. In support of these data, in some studies, delayed introduction of enteral feeds beyond the first few days after birth protected against NEC [44]. Other studies showed that adoption of standardized, cautious feeding regimens where feeding volume was increased by < 24 mL/kg body weight each day lowered the risk of NEC [95, 105]. In the neonatal research network of the National Institute of Child Health and Development, Centers where enteral feedings were introduced at an earlier postnatal age and were advanced rapidly showed a higher incidence of NEC than institutions with more conservative feeding practices [55]. Based on data from these and other observational studies, most care-providers in neonatology adopted a very conservative approach to enteral feeding [105].

In contrast to observational/anecdotal data, early introduction or rapid advancement of feedings has not been shown to increase the incidence of NEC in randomized studies. In meta-analysis [70] of 4 randomized controlled trials (RCTs) [2, 12, 41, 52] comparing infants who received slow advancement of feedings (daily increments of 15–20 mL/kg) vs. those who were advanced rapidly (30–35 mL/kg/day), there was no difference in the incidence of NEC (typical relative risk (RR): 0.91, 95 % confidence interval (CI): 0.47–1.75) or all-cause mortality (RR: 1.43, 95 % CI: 0.78–2.61). Infants who had slow rates of feed volume advancement took longer to regain birth weight (median difference 2–6 days) and to establish full enteral feeding (median difference 2–5 days). Similarly, the protective effects of delayed introduction of enteral feedings, if any, were not detected in RCTs. In meta-analysis [67] of 5 RCTs, [24, 57, 58, 66, 88] delayed feedings did not reduce the risk of NEC [RR: 0.89, 95 % CI: 0.58–1.37] or all-cause mortality (RR: 0.93, 95 % CI: 0.53–1.64). Infants who had delayed introduction of enteral feeds took longer to establish full enteral feeding (reported median difference 3 days).

Minimal enteral feeding as an alternative to enteral fasting in premature infants Based on data from physiological and pre-clinical studies, minimal enteral feeding can stimulate gut motility and gastrointestinal hormone release, reduce the incidence of dysmotility and feeding intolerance, and thereby reduce the time taken to reach full enteral feeds. Enteral feedings may also reduce the incidence of complications associated with enteral fasting such as hyperbilirubinemia (related to increased enterohepatic circulation of bilirubin) or with parenteral nutrition such as infections and metabolic complications [107].

In most nurseries, minimal enteral feeding is defined as enteral administration of 12–24 mL/kg/day of expressed breast milk or formula. If more than 25 % of the patient's nutritional needs are administered enterally, the feeding is no longer considered 'trophic'. In a 1-kg infant, 20 mL/kg/day of enteral feedings represent about 5 % of the total volume of amniotic fluid that a gestational age-matched fetus would ingest each day *in utero*. Although the preterm gut may be able to handle larger volumes, minimal feeding strategies limit the feed volumes in view of the higher osmolality and protein/lipid concentration in milk/formula than amniotic fluid, which may affect the tolerance to enteral feeding.

Preclinical studies on the effects of enteral fasting Animal studies emphasize the importance of the first few postnatal weeks as a critical time for the growth and development of the gastrointestinal tract. In fetal pigs, the small intestine of responds rapidly to the introduction of oral colostrum or milk formula with large increases (50–75 %) in intestinal weight, similar to those in preterm and term newborn pigs receiving sow's colostrum [18]. This gastrointestinal growth response is not seen in enterally-fasted newborn piglets maintained on total parenteral nutrition. These findings are consistent with rapid growth of the small intestine seen in human infants during the early neonatal period [5, 99].

Kansagra et al. [42] showed that lack of enteral nutrition in piglets led to gut mucosal atrophy with decreased jejunal mass (34.8 %), villus height (44.4 %), and villus area (56.1 %) of TPN-fed piglets compared to enterally-fed newborn piglets.

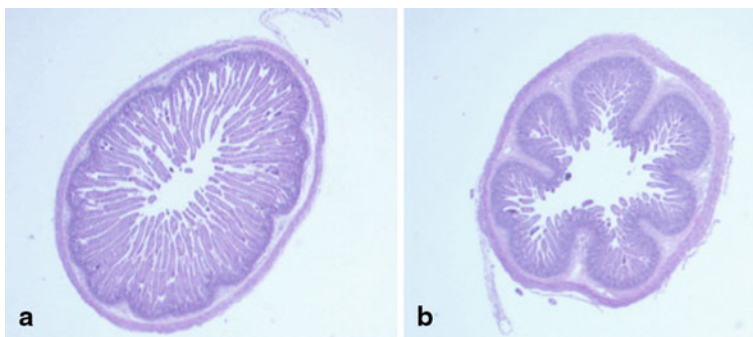


Fig. 2.1 Photomicrographs of jejunal tissue sections (hematoxylin and eosin; magnification 62.5 \times) from (a) enterally-fed newborn piglets; and (b) enterally-fasted piglets maintained on parenteral nutrition. Enteral fasting was associated with mucosal atrophy and loss of villus height (images courtesy Dr. Douglas Burrin, Baylor College of Medicine, Houston, Texas)

The absence of luminal nutrition in the intestine has also been associated with abnormal permeability to macromolecules, compromised barrier function, and eventually, loss of mucosal integrity [42, 106]. These changes, in turn, increase the risk of bacterial translocation and gut-derived sepsis [82]. In newborn piglets, gut mucosal atrophy ensues in the setting of partial/total absence ($< 60\%$ total caloric intake) of enteral nutrition and is characterized by reduced villus height (Fig. 2.1), decreased crypt cell proliferation, and increased enterocyte apoptosis [8, 40]. TPN-induced mucosal atrophy is also associated with lymphocyte activation, [83] increased expression of adhesion molecules, [23, 48, 53] recruitment of neutrophils, and increased expression of inflammatory cytokines [13, 29, 89].

Studies from preterm animals show that early initiation of feeds from birth with animal colostrum results in an enhanced resistance to NEC [29]. Early introduction of minimal enteral feeding have been shown to promote intestinal motility, peristalsis, and enzymatic activity, augment intestinal blood flow, maintaining intestinal barrier function, reduction of infections and promoting development of beneficial gut microflora [11, 39, 54, 100].

4 Clinical Studies on Minimal Enteral Feeding

Minimal enteral feeding vs. enteral fasting in the first week after birth Several observational studies and clinical trials have examined minimal enteral feeding (Table 2.1). In 2005, Tyson and Kennedy [46] reviewed 11 studies of minimal enteral feeding. In 10 studies that compared minimal enteral feeding vs. enteral fasting, [15, 33, 45, 49, 50, 59, 61, 79, 84, 91] they noted that the minimal feeding group took fewer days to reach full enteral feeds (weighted mean difference (WMD) = 2.6 days), had fewer days when feedings were held (WMD = 3.1 days), and a shorter length of hospital stay (WMD = 11.4 days). There was no effect on

Table 2.1 Minimal enteral feeding: quality of evidence

Authors, Year	Description of study	Outcome/Results	Comments on study design and quality of evidence
Leaf, 2012 [24]	Infants < 35 weeks gestational age, birth weight < 10 percentile, and abnormal antenatal umbilical artery Doppler randomized to early feeding on day 2 (<i>n</i> = 201) <i>vs.</i> delayed on day 6 (<i>n</i> = 201).	Full feeds achieved earlier in early feeding group (median age 18 days <i>vs.</i> 21 days) (hazard ratio: 1.36 [95 % CI 1.11–1.67]). No difference in the incidence of NEC.	Randomized, blinded, all subjects included in analysis.
Mosqueda, 2008 [21]	Minimal enteral feeding of expressed breast milk or formula 2 mL every 4 hrs from day 2–7 (<i>N</i> = 41) <i>vs.</i> enteral fasting (<i>N</i> = 43). Both groups received progressive enteral feeds from day 8, increasing by 10 mL/kg/day.	No difference in growth patterns, feeding tolerance, mortality, length of stay, incidence of sepsis and NEC between groups.	Randomized, but not blinded and incomplete follow-up.
Van Elburg, 2004 [104]	Minimal enteral feeding 0.5–1 mL every 2 h with breast milk/preterm formula from day 2–5 (<i>N</i> = 28) <i>vs.</i> enteral fasting (<i>N</i> = 28). Both groups received progressive enteral feeds from day 8, increasing by 10 mL/kg/day.	No difference in feeding tolerance, growth, incidence of NEC, and postnatal maturation of gut mucosal permeability as measured by lactose: mannitol absorption test.	Randomized, but not blinded and incomplete follow-up.
de PIPAON, 2003 [93]	Minimal enteral feeding of 10 mL/kg/day on day 1, then 20 mL/kg/day through until day 7 (<i>N</i> = 24) <i>vs.</i> enteral fasting for 7 days (<i>N</i> = 12).	Intestinal maturation measured as leucine uptake by splanchnic tissues. Minimal enteral feeding increased leucine uptake by the splanchnic tissue.	Randomization unbalanced (larger minimal enteral feeding group). Not all infants included in analysis. Biochemical outcome.
McLure, 2000 [84]	Minimal enteral feeding group received 0.5–1 mL/h breast milk/preterm formula from day 3 until discontinuation of assisted ventilation (<i>N</i> = 48). Control group was enterally-fasted (<i>N</i> = 52). After ventilation was stopped, feeds were started at 1 mL/kg/h and increased by 1 mL/kg/h every 8–12 h	Minimal enteral feeding group had better weight gain and increase in head circumference, fewer episodes of sepsis, decreased duration of parenteral nutrition, oxygen use, and length of hospital stay.	Randomized, blinded and all subjects included in analysis.

Table 2.1 (continued)

Authors, Year	Description of study	Outcome/Results	Comments on study design and quality of evidence
Schanler, 1999 [31]	Infants 26–30 weeks. Minimal enteral feeding ($N = 82$) 20 mL/kg/day of expressed breast milk or half-strength preterm formula from day 4–14 after birth vs. enteral fasting ($N = 89$). Minimal enteral feeding and fasting groups randomized to continuous vs. bolus feeds.	Time to full oral feeding similar in both groups. Minimal enteral feeding associated with better mineral retention, and shorter intestinal transit times. Bolus feeding associated with less feeding intolerance and better weight gain than the continuous method.	Randomized with complete follow-up but not blinded.
Becerra et al. 1996 [50]	Minimal enteral feeding with breast milk or preterm formula at 20–25 mL/kg/day ($n = 96$) vs. enteral fasting until 6–8 days post-natal ($N = 94$). Also included an arm with “healthy” VLBW infants	Minimal enteral feeding group had higher early weight gain, less hours of NPO, and less hyperglycemia than controls. No difference in the number of days to regain birth weight, weight on postnatal day 60, NEC, sepsis, and overall mortality.	Although all subjects were included in the analysis, study was non-blinded and the methods of randomization were not defined.
Troche, 1995 [72]	Infants 25–30 wks. Minimal enteral feeding group received expressed breast milk/standard formula from 24 h after birth at a rate of 0.5–1 mL/h until umbilical artery catheter was removed ($N = 16$) vs. enteral fasting ($N = 13$). Both groups received parenteral nutrition starting from day 3.	Minimal enteral feeding group required fewer days to reach full enteral feeds and had better weight gain. Minimal enteral feeding was well-tolerated in critically-ill VLBW infants requiring mechanical ventilation.	Randomization unclear, not blinded and not all subjects included in analysis.
Davey, 1994 [45]	Minimal enteral feeding group received 2–5 mL every 2 hrs of 1/4 strength formula from 2 days ($N = 31$) vs. late enteral group which received feedings from day 5 ($N = 31$). Both groups had same volume of feeds and rate of advancement.	Minimal enteral feeding group had fewer days on parenteral nutrition, fewer interruptions in feedings, fewer sepsis evaluations, and fewer central lines. No difference in weight gain, NEC, mortality, or age at discharge.	Randomized and blinded in radiologic assessment but not blinded in clinical assessment. Not all patients were included in analysis.
Meetze, 1992 [62]	Minimal enteral feeding group received preterm formula from day 3 at 2.5 mL/kg/day and advancing to 22 mL/kg/day on day 14 ($N = 22$) vs. enteral fasting ($N = 25$). Both groups received progressive enteral feeds from day 15.	Minimal enteral feeding group had improved feeding tolerance after day 20 and a faster rise in serum gastrin. No difference in weight gain, frequency of feeding complications.	Randomization unclear, not blinded and not all subjects included in analysis.

Table 2.1 (continued)

Authors, Year	Description of study	Outcome/Results	Comments on study design and quality of evidence
Berseth, 1992 [61]	<p>Infants 28–32 weeks on mechanical ventilation. Minimal enteral feeding group received a standard formula at 24 mL/kg/day from day 3–5 until day 10–14 ($N = 14$) vs. enteral fasting group ($N = 13$) that remained NPO until day 10–14. Both groups received 150 mL/kg/day total fluids.</p> <p>Minimal enteral feeding group ($N = 19$) from 48 hrs of life at 15–20 mL/kg/day using diluted preterm formula vs. enteral fasting ($N = 20$) until 9 days after birth.</p>	Minimal enteral feeding group tolerated full oral feeds sooner, had fewer days of feeding intolerance, and had shorter length of hospital stay. These infants also showed more mature motor patterns and higher plasma levels of gastrin and gastric inhibitory peptide.	Although all subjects included in analysis, study was non-blinded; methods of randomization not defined.
Dunn, 1988 [14]	Minimal enteral feeding group ($N = 19$) from 48 hrs of life at 15–20 mL/kg/day using diluted preterm formula vs. enteral fasting ($N = 20$) until 9 days after birth.	Minimal enteral feeding group took fewer days to reach full enteral feedings, spent less time under phototherapy, had less cholestasis, and lower peak direct bilirubin levels.	Not randomized, not blinded, and not all subjects included in analysis.
Slagle, 1988 [16]	Infants 500–1500g, < 33 weeks. Minimal enteral feeding group ($N = 22$) received 12 mL/kg/d breast milk feedings from day 8 to day 18 vs. enteral fasting ($N = 24$).	Minimal enteral feeding group tolerated feeds better with fewer days when feedings were withheld. More infants reached full enteral feedings by 6 weeks.	Randomized, but not blinded and not all subjects included in analysis.
Khayata, 1987 [67]	$N = 12$, VLBW infants. Minimal enteral feeding group received standard formula starting at < 96 hrs of age at 12 mL/kg/day, increased to 24 mL/kg/day on day 2, 36 mL/kg/day on day 3–5. Late group remained NPO until day 10 and then fed using same schedule.	No difference in weight gain during the first six weeks after birth	Methodological details missing in abstract; unclear if subjects randomized; not blinded.
Ostertag, 1986 [52]	Infants < 32 weeks and < 1500 g. Minimal enteral feeding group ($N = 18$) fed enterally at 1 mL/h, starting with sterile water on day 1 and progressing to 2.5 % dextrose, 1/2 strength formula, and full strength formula over 7 days. Control group stayed NPO for 7 days followed by progressive enteral feeds increasing by 10 mL/kg/day ($N = 20$).	No difference in incidence of NEC	Unstated randomization, not blinded, but all subjects included in analysis.

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