

## CURRENT TOPIC

## Early enteral feeding of the preterm infant

Questions about when, how, and what to feed the preterm baby elicit many different answers. Balancing the risks of enteral feeding with those of parenteral nutrition is not easy. In contrast with the sophistication of clinical cardiorespiratory monitoring, the day to day assessment of gastrointestinal function is still largely dependent on clinical observation. Moreover the population at risk is extremely heterogeneous with respect to both the prevalence of comorbidity and developmental stage, particularly, in this context, the maturation of intestinal motility. Enteral feeding involves many potentially confounding interventions: route chosen, postnatal or postconceptional age at initiation, frequency of administration, amount given, rate of advancement, and, not least, choice between human milk and formula. Given the complexity of the problem, the small size of most controlled studies, problems with blinding, and the difficulties of defining and measuring outcome, it is hardly surprising that confusion exists.

### Enteral or parenteral feeding?

The spectre of necrotising enterocolitis (NEC) is the dominant argument for postponing enteral feeding, yet NEC can occur in babies fed parenterally. The risk of sepsis and other complications during total parenteral nutrition (TPN) is high and may more than offset any reduction in the risk of NEC.<sup>1</sup> TPN also provides certain important nutrients less effectively, notably vitamin A, glutamine, calcium, and phosphorus.

On the other hand, enteral feeding (with milk, not water<sup>2</sup>) in the first five days of life promotes endocrine adaptation and the maturation of motility patterns,<sup>3</sup> provides luminal nutrient, and probably benefits immune function.<sup>4</sup> Potential clinical benefits are therefore earlier tolerance of enteral feeds, reduced risk of infection, and earlier discharge.

### When to begin feeds: “trophic feeding”

Trophic feeding describes the provision of milk feeds in subnutritional quantities for a predetermined period. It has also been termed “minimal enteral nutrition” and “gut priming”. A systematic review of studies published to 1997 concluded that it reduced the period elapsing before full tolerance of enteral feeds and shortened hospital stay without increasing incidence of NEC.<sup>5</sup> A recently published randomised controlled trial of 100 infants weighing < 1750 g at birth has confirmed this.<sup>6</sup> Babies were randomly allocated to TPN alone or together with 0.5–1 ml/h milk until withdrawal of ventilation. The trophic feeding group showed, among other benefits, greater energy intake associated with more rapid weight gain and head growth. They were at no greater risk of NEC and significantly less likely to develop sepsis.

In a more complex study, Schanler *et al*<sup>7</sup> have unravelled the potentially confounding effects of “priming” (feeding 20 ml/kg/day between days 4 and 14 of life), feeding method (bolus or continuous intragastric), and diet (preterm formula or fortified mother’s milk).<sup>7</sup> By stratifying for diet and gestation, and applying a 2 × 2 randomised design, they were able to separate the effects of priming and

feeding method on the time taken to establish full oral feeding. Other than a small increase in calcium retention, no clinical benefits were associated with priming, but feed frequency (bolus or continuous) and diet were more influential. One unexpected additional finding was that the “primed” group ultimately received more human milk—perhaps because mothers felt more motivated to express although this was not directly shown. Neither of these recent studies has confirmed a reduced incidence of hyperbilirubinaemia associated with trophic feeding.<sup>8</sup> This is disappointing because cholestasis associated with TPN remains an important clinical problem.

It is difficult to explain the apparent discrepancy between the findings of these two recent studies. Similar populations seem to have been studied, at least in terms of gestational age and birth weight, but there may have been subtle differences in the choice of primary outcome measures and differences in the definition and management of feed intolerance (by their very nature these studies cannot be blinded). The central point is that neither study showed an increase in the incidence of NEC associated with “trophic” feeding. This does, however, beg a question as to whether one may just as well increase feed volume as tolerated, rather than prolong feeding with subnutritional quantities.

### Advancing the volume of enteral feeds

Clinical concern about advancing the volume of feed has long focused on NEC.<sup>9</sup> A systematic review<sup>10</sup> failed to show a significant relation between “rapid” advancement (up to 35 ml/kg/day) and NEC, although the only randomised study then published in full was extremely small (29 patients).<sup>11</sup> The full findings from a much larger study (included as an abstract in the systematic review) have now been published.<sup>12</sup> From the third day of life, 185 formula fed babies under 35 weeks of gestation were randomly allocated to receive 20 or 35 ml/kg/day with daily increments of 15 or 35 ml/kg thereafter. There was no statistically significant difference in the incidence of NEC overall; in fact more “slow” babies developed the condition, particularly among those < 1000 g (9/43 “slow” *v* 3/33 “fast”).

Evidence from randomised controlled trials therefore suggests that introducing enteral feeds, trophic or otherwise, in the first four days of life has no effect on the incidence of NEC. This is a “broad brush” conclusion, however, as several exclusion criteria were applied in the studies described. For example, Rayyis *et al*<sup>12</sup> excluded babies receiving pressor agents to sustain blood pressure, although they did include small for dates and ventilated infants. More data are needed on high risk groups who may not always follow this trend. Better ways of predicting risk are also needed.

### Frequency of feeding

Continuous tube feeding of preterm infants is less commonly practised than some years ago. The reasons are many: adsorptive loss of nutrients, increased microbial contamination, and less physiological profiles of circulating gut derived neuroendocrine peptides. Although energy

expenditure is higher during intermittent feeding,<sup>13</sup> clinical trials have failed to show any adverse effect on growth.<sup>14</sup>

Clinical experience suggests that administration by gravity infusion over 15–20 minutes is common in current practice, but antroduodenal manometry studies question the wisdom of this. Term and preterm infants respond differently to a rapid bolus feed. The former increase motor contractions in the upper gastrointestinal tract, whereas the latter develop quiescence. When the same volume of feed (20 ml/kg) was infused intragastrically into 32–35 week gestation babies over two hours rather than 20 minutes, there was no inhibition of gastrointestinal motility and gastric residual volumes were smaller.<sup>15</sup> This would suggest that slow administration of bolus feeds may have advantages.

Whether such physiological data extrapolate to improved outcome is another question. Two recently published randomised studies have re-examined the effects of intermittent and continuous tube feeding, failing to identify differences in clinical outcome.<sup>16 17</sup> In one, 82 babies weighing < 1500 g at 27–34 weeks of gestation were stratified into three birthweight groups (< 1000, 1000–1249, and 1250–1499 g) and randomly allocated to continuous or three hourly tube feeding.<sup>17</sup> No differences in the length of hospital stay, macronutrient retention, or growth rates were found, but 11 infants (eight from the intermittent group) were excluded from the analysis. In three of these (all < 1000 g), “feeding intolerance” was given as a reason, and, in another “gastric perforation”. As these could be considered pragmatic study outcomes, the validity of a “no difference” conclusion seems questionable.

By contrast, another study<sup>7</sup> pursued intention to treat analysis and found that three hourly feeds (as a bolus over 20 minutes) were associated with significantly less feeding intolerance (defined on the basis of gastric residual volume) than continuous feeding. This translated into more rapid weight gain and earlier discharge from hospital.

### Diet: human milk or formula

Of the studies mentioned above, three<sup>12 16 17</sup> recruited formula fed babies only, but two<sup>6 7</sup> included some who were fed on human milk. One stratified for this at randomisation and treated human milk intake as a covariate in the analysis.<sup>7</sup> Regardless of other feeding interventions, use of human milk was associated with a significantly reduced incidence of NEC (and indeed other forms of sepsis<sup>18</sup>). This is in keeping with other work that showed interaction between diet and postnatal age at the introduction of feeds, suggesting that delay in starting formula, but not human milk, may be protective.<sup>19</sup> Schanler *et al*<sup>7</sup> commented that differences in tolerance between feeding methods were unrelated to diet, which seems surprising. In a straightforward randomised comparison, babies fed on human milk tolerated feeds at an earlier postnatal stage than formula fed babies, allowing TPN to be withdrawn considerably sooner.<sup>20</sup> It may be relevant that Schanler *et al* used “fortified” breast milk, although this has not been shown ultrasonographically to affect gastric emptying,<sup>21</sup> nor was feed intolerance associated with “fortification” in the largest randomised controlled study of this practice.<sup>22</sup>

The safety and benefit associated with routinely adding “fortifiers” to human milk is still, however, open to question.<sup>23</sup> In the only large published intention to treat study, babies who received liquid fortifier were at increased risk of sepsis, yet showed no short or long term growth advantage.<sup>22</sup> There is increasing evidence that even large discrepancies in neonatal growth rate are not reflected in size at school age,<sup>24</sup> which may better reflect growth and nutrition after discharge. Indeed, when human milk (as

opposed to standard infant formula) has been given, there seems little evidence that low nutrient intake and slower neonatal growth adversely affects neurodevelopmental outcome either.<sup>25</sup>

### Summary

Recently published randomised controlled trials provide no evidence to support the practice of postponing enteral feeding to reduce the incidence of NEC. On the contrary, feeding within the first few days of life yields demonstrable benefits such as reduced incidence of sepsis and earlier discharge from hospital. Although manometry suggests that slow infusion of feeds is associated with improved gastric emptying, clinical trials suggest that “bolus” three hourly feeding is if anything less likely to result in feed intolerance than continuous infusion. Use of human milk reduces the risk of NEC and infection irrespective of other feeding interventions, although routine “fortification” may prejudice this while offering no proven long term growth or developmental advantage.

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