

ORIGINAL ARTICLE

Minimal enteral feeding, fetal blood flow pulsatility, and postnatal intestinal permeability in preterm infants with intrauterine growth retardation

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Arch Dis Child Fetal Neonatal Ed 2004;**89**:F293–F296. doi: 10.1136/adc.2003.027367

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Accepted
16 September 2003

Objective: To study the effect of minimal enteral feeding (MEF) on intestinal permeability and feeding tolerance in preterm infants with intrauterine growth retardation (gestational age < 37 weeks, birth weight for gestational age $p < 10$). Furthermore, to determine whether fetal blood flow pulsatility or intestinal permeability predict feeding tolerance in these infants.

Design: Randomised controlled trial.

Methods: Within 48 hours of birth, infants were randomised to MEF or no enteral feeding (NEF) for five days in addition to parenteral feeding. Intestinal permeability was measured by the sugar absorption test before (SAT1) and after (SAT2) the study. The sugar absorption test measured the urinary lactulose/mannitol (LM) ratio after oral ingestion of a solution (375 mosm) containing mannitol and lactulose. Charts of all infants were assessed for measures of feeding tolerance. Fetal blood flow pulsatility index (U/C ratio) was measured within the seven days before birth.

Results: Of the 56 infants enrolled, 42 completed the study: 20 received MEF and 22 NEF. The decrease in LM ratio (LM ratio 1 – LM ratio 2) was not significantly different between the two groups (0.25 v 0.11; $p = 0.14$). Feeding tolerance, growth, and incidence of necrotising enterocolitis were not significantly different between the two groups. Neither the U/C nor the LM ratio 1 predicted feeding tolerance.

Conclusions: The results suggest that MEF of preterm infants with intrauterine growth retardation has no effect on the decrease in intestinal permeability after birth. Neither fetal blood flow pulsatility nor intestinal permeability predicts feeding tolerance.

In fetal sheep with intrauterine growth retardation (IUGR) caused by placental insufficiency, fetal blood flow is redistributed.¹ Blood flow to heart, brain, and adrenals is increased in compensation, while other organs including the gastrointestinal tract are relatively hypoperfused.² Fetal blood flow pulsatility shows this effect by changes in flow velocity waveforms in the cerebral arteries and umbilical arteries.^{3,4} Flow velocity waveforms can be qualitatively analysed using the pulsatility index (PI), defined as the difference between peak systolic and end diastolic value divided by the time average velocity.⁵ Redistribution of fetal blood flow, also called brain sparing, is characterised by the increase in umbilical artery/middle cerebral artery PI ratio.⁶

As a consequence of brain sparing, preterm infants with IUGR are thought to have impaired gut function after birth, which may result in problems ranging from temporary intolerance of enteral feeding to full blown necrotising enterocolitis (NEC). The development of a suitable feeding strategy would be helped by identification of infants at risk of gastrointestinal disturbances before birth. A few studies have investigated the relation between fetal blood flow pulsatility and gastrointestinal disturbances.^{7–12}

As enteral feeding may increase the risk of NEC, its initiation is often postponed. Minimal enteral feeding (MEF) has recently been introduced as a strategy to improve feeding tolerance and to prevent complications of prolonged parenteral nutrition, such as gut mucosa atrophy.¹³ Studies of MEF in preterm infants have shown varying effects on clinical outcomes such as feeding tolerance and growth.^{14–21} In addition, the mechanism for the effect of MEF is not known. Assessment of the functional integrity of the small

bowel, as measured by intestinal permeability to macromolecules, may help to elucidate the effect of MEF on the gut. In addition, intestinal permeability may provide a guide for timing the introduction of enteral feeding. In previous studies in children and adults, we measured intestinal permeability by the sugar absorption test (SAT) using lactulose and mannitol.^{22–24} In a recent study, we found that measurement of intestinal permeability by SAT is feasible in infants with a gestational age of 26–40 weeks.²⁵ Furthermore, we found that intestinal permeability clearly decreased during the first days of life.

We hypothesised that MEF of preterm infants with IUGR has a positive effect on intestinal permeability, reflected by a larger decrease in intestinal permeability in the first days of life. To test this hypothesis, we performed a randomised clinical trial of MEF for five days. We evaluated the functional integrity of the gut, reflected by intestinal permeability, and clinical outcome, reflected by feeding tolerance, growth, and the development of NEC. Furthermore, we determined whether fetal blood flow pulsatility or intestinal permeability could predict feeding tolerance after birth.

PATIENTS AND METHODS

Study population

From January 1998 to November 2000, all preterm infants with a gestational age less than 37 weeks, a birth weight

Abbreviations: MEF, minimal enteral feeding; NEC, necrotising enterocolitis; NEF, no enteral feeding; PI, pulsatility index; SAT, sugar absorption test; IUGR, intrauterine growth retardation

< 2000 g, and birth weight for gestational age below the tenth centile,²⁶ admitted to the neonatal intensive care unit of the Isala Clinics location Sophia (a tertiary referral centre) were eligible to participate in the study. Exclusion criteria were major congenital anomalies and anomalies of the gastrointestinal tract. The study was approved by the ethics committee of the Isala Clinics Zwolle.

If written informed parental consent was obtained, infants were assigned randomly by selection of cards in sealed envelopes to one of two feeding groups. One group received MEF (birth weight < 1000 g: daily 12 × 0.5 ml breast milk or preterm formula; birth weight > 1000 g: daily 12 × 1 ml breast milk or preterm formula (Nenatal; Nutricia Nederland BV, Zoetermeer, the Netherlands)); the other group received no enteral feeding (NEF) for five days. Nursing and medical staff as well as the researchers were aware of group assignment. All infants received parenteral feeding according to the standard protocol.

The primary outcome of the study was functional integrity of small bowel as reflected by intestinal permeability. Furthermore, we assessed feeding tolerance (time to reach full enteral feeding, number of days feed withheld), growth (days to regain birth weight, weight as percentage of birth weight on day 28), and adverse outcome (NEC Bell's ≥ stage II). Finally, we determined whether fetal blood flow pulsatility (U/C ratio) or intestinal permeability (measured within 48 hours of birth) could predict feeding tolerance.

Intestinal permeability

Intestinal permeability was measured by SAT as previously described.²⁵ In short, after instillation of the test solution (2 ml/kg by nasogastric tube), urine was collected for six hours. As a preservative, 0.1 ml chlorohexidine digluconate 20% was added to the urine. Lactulose and mannitol concentrations (mmol/mol creatinine) were measured by gas chromatography as previously described,²⁷ and the lactulose/mannitol (LM) ratio was calculated. The SAT was performed before (SAT1) and after (SAT2) five days of intervention.

Fetal blood flow pulsatility

Fetal blood flow pulsatility was measured based on obstetric decisions including evaluation of (suspected) IUGR. Only blood flow pulsatility measurements of the umbilical and middle cerebral artery performed within the seven days before birth were acceptable for the study. The last measurement before birth was used for analysis. Blood flow pulsatility was measured with the pregnant woman in a semirecumbent position, using a colour Doppler ultrasound system (ATL 5000 HDI; Bothell, Washington, USA). Measurements were performed during a steady state (fetal apnoea, physiological fetal heart rate, and no fetal movements). Flow velocity waveforms were analysed by the PI, defined as the difference between peak systolic and end diastolic value divided by the time average velocity.⁵ Distribution of fetal blood flow was characterised by the umbilical artery/middle cerebral artery PI ratio (U/C ratio).⁶

Data analysis

Data were analysed using SPSS 9.0 (SPSS Inc, Chicago, Illinois, USA). Data are expressed as median values and range. Student's *t* test and the χ^2 test were used for statistical comparison of clinical characteristics. A Mann-Whitney *U* test was performed to compare LM ratios of the MEF and NEF group. Wilcoxon signed ranks test analysed the difference between SAT1 and SAT2. Linear regression was used to calculate the predictive value (expressed as variance) of fetal blood flow pulsatility and intestinal permeability as measures of clinical outcome. $p < 0.05$ was considered significant.

RESULTS

Fifty six infants were included in the study. The flow of patients is shown in the trial profile (fig 1). The data for 14 infants were not analysed because of early transfer to another hospital, congenital cytomegalovirus infection, death before the end of the study, or insufficient urine collection during the SAT (fig 1). The median gestational age was 210 days (range 184–254) and birth weight was 900 g (range 625–1935). The birth weight of all infants was < p10. Patient characteristics were similar in the two groups (table 1).

Table 2 shows the results of the SAT. In both the NEF and MEF group, LM ratio 1 as higher than LM ratio 2 ($p = 0.006$ and $p = 0.001$ respectively). The decrease in LM ratio (LM ratio 1 to LM ratio 2) was not significantly different in the two groups ($p = 0.14$). The decrease in LM ratio was due to decreased permeability to lactulose (mmol/mol creatinine) in both the MEF group (301 v 109, $p = 0.002$) and NEF group (270 v 132, $p = 0.03$). The decrease in LM ratio was not due to increased permeability to mannitol (mmol/mol creatinine) in the MEF group (741 v 925, $p = 0.41$) or the NEF group (816 v 692, $p = 0.73$).

Feeding tolerance, growth, and the incidence of NEC were not significantly different in the two groups (table 3). One patient in the MEF group was diagnosed with an immature bowel syndrome, requiring an ileostomy. The patient had a very long hospital stay, and time to reach full enteral feeding was 46 days. As the overall results were not different without this patient, the patient was not excluded from analysis.

Fetal blood flow pulsatility was measured in 25/42 infants. Neither the U/C ratio nor LM ratio 1 had predictive value for time to reach full feeding ($r^2 = 0.01$, $p = 0.55$; $r^2 = 0.07$, $p = 0.11$ respectively).

DISCUSSION

In our randomised clinical trial in preterm infants with IUGR, we found that MEF for five days did not influence the decrease in intestinal permeability in this period compared with NEF. Furthermore, although not the primary outcome of our study, MEF had no effect on feeding tolerance or growth.

The few studies on the effect of (minimal) enteral feeding on intestinal permeability show conflicting results.^{28–31} This may largely be caused by differences in study design, use of different markers, and timing of intestinal permeability tests.^{28–29} In a previous study, we found that intestinal permeability, as measured by the same SAT, decreased between the first test (within 48 hours of birth) and the second test (five days later) independent of gestational age and birth weight.²⁵ This decrease in intestinal permeability may reflect rapid postnatal adaptation of the gut and may be part of the so called gut closure. Although intestinal permeability in preterm infants was not related to gestational age, intestinal permeability was higher in preterm infants than in term infants if measured within 48 hours of birth.²⁵ Our results are in line with results of studies of Weaver *et al*²⁸ and Beach *et al*,²⁹ although differences exist in study populations (gestational age, antenatal steroids, etc) and the test methods (steady state versus bolus). In contrast, the studies of Rouwet *et al*³⁰ and Shulman *et al*³¹ showed that intestinal permeability in preterm infants increases during respectively the first 7 and 28 days after birth. Shulman *et al* also found that MEF decreased intestinal permeability compared with NEF. In the study of Rouwet *et al*, enteral feeding was postponed until 7 days age. This may explain the increase in intestinal permeability. In a study of infants ≥ 34 weeks of gestation receiving extracorporeal membrane oxygenation, no adverse effect of enteral feeding on intestinal permeability was found.³² In this study, we found a similar decrease in intestinal permeability to that in our previous

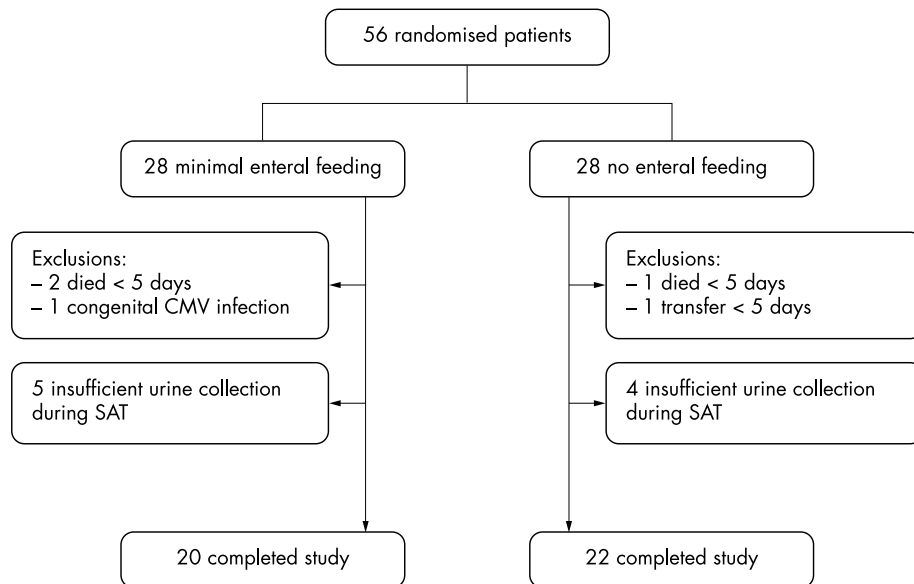


Figure 1 Trial profile. CMV, Cytomegalovirus; SAT, sugar absorption test.

study,²³ suggesting that MEF has no adverse effect on intestinal permeability.

Although not the primary outcome of our study, MEF had no effect on feeding tolerance and growth in preterm infants with IUGR. This is in contrast with other randomised clinical trials which showed a positive effect of MEF on the time to reach full enteral feeding,^{14, 21} length of time feed withheld,^{14, 20} time to regain birth weight,¹⁴ and hospital stay.¹⁴ However, a recent Cochrane Review of nine randomised clinical trials of minimal enteral nutrition in parenterally fed neonates showed no convincing evidence for the beneficial effects of MEF in very low birthweight infants.³³ Moreover in this meta-analysis, the possibility that MEF might increase the incidence of NEC could not be excluded.³³ In our study, there was only one case of NEC in the NEF group. Although our study was the second largest to date, a larger sample size is needed to draw conclusions about the effect of MEF on measures of clinical outcome.

Preterm infants with IUGR often have prenatal haemodynamic disturbances such as absent and/or reversed end diastolic velocities in the umbilical artery, decreased PI of the middle cerebral artery, and/or increased PI of the umbilical artery.^{4, 34} These prenatal haemodynamic disturbances have been associated with increased perinatal mortality^{7, 33} and morbidity such as intracranial haemorrhage,^{7, 8} infant respiratory distress syndrome,⁷ gastrointestinal disturbances,^{11, 12} and NEC.⁷⁻⁹ However, the study of Mihatsch *et al*¹⁰ did not show any association between increased umbilical artery resistance and feeding tolerance. In our study, fetal blood

flow pulsatility, reflected by U/C ratio, had no predictive value for feeding tolerance, nor did the LM ratio within 48 hours of birth. Several factors may explain our findings. Firstly, we only studied infants with severe IUGR and greatly increased U/C ratio and no infants with normal PI values (compared with the reference values as described by van Eyck and Reuwer³⁵). Secondly, the U/C ratio may be a good marker of postnatal gut function only in infants with antenatal absent or reversed flow in the umbilical artery, who have an increased risk of NEC.^{7, 8} Thirdly, intestinal permeability as measured by SAT may be influenced by various other factors such as postnatal respiratory and circulatory problems and infections, which may mask the possible relation of fetal blood flow pulsatility and postnatal intestinal permeability.

In summary, our study showed no additional effect of MEF on the decrease in intestinal permeability after birth in preterm infants with IUGR. Fetal blood flow pulsatility or intestinal permeability measured within 48 hours after birth had no predictive value for feeding tolerance in preterm infants with IUGR. Future studies on the effect of MEF on clinical outcome in preterm infants with IUGR should focus on a sufficiently large sample size and functional development of the immature gastrointestinal tract.

ACKNOWLEDGEMENTS

Supported in part by a grant from Nutricia Nederland BV, Zoetermeer, the Netherlands. We thank all parents and their infants who participated in this study.

Table 1 Patient characteristics

	MEF (n = 20)	NEF (n = 22)
Gestational age (weeks)	29.3 (26.3–34.1)	30.4(27.7–36.3)
Birth weight (g)	890 (650–1270)	900 (625–1935)
Asymmetric growth retardation*	13/20	14/22
Apgar 5 min<6	2/20	2/22
pH umbilical artery <7.10	1/20	1/22
Mechanical ventilation	14/20	11/22
Clinical risk index for babies	3 (1–10)	2 (0–12)

Data are expressed as median (range) or numbers.
*Defined as birth weight for gestational age < p10 and head circumference for gestational age > p10 at birth.
MEF, Minimal enteral feeding; NEF, no enteral feeding.

Table 2 Results of the sugar absorption test (SAT) before (lactulose/mannitol (LM) ratio 1) and after (LM ratio 2) minimal enteral feeding (MEF) or no enteral feeding (NEF) (mmol/mol creatinine)

	MEF (n = 20)	NEF (n = 22)
LM ratio 1	0.32 (0.02–0.90)	0.26 (0.02–1.1)
LM ratio 2	0.11 (0.03–0.42)*	0.15 (0.00–0.46)*
LM ratio 1–	0.25 (–0.39–0.62)†	0.11 (–0.11–0.84)
LM ratio 2		

Data are expressed as median (range).
*p = 0.001 and p = 0.006 LM ratio 2 v LM ratio 1 in MEF and NEF respectively.
†p = 0.14 MEF v NEF.

Table 3 Feeding tolerance and growth

	MEF (n = 20)	NEF (n = 22)	p Value
Days to reach full enteral feeding	13 (7–46)	13 (9–23)	0.32
Days NPO*	0 (0–15)	0 (0–3)	0.16
Days to regain birth weight	11 (5–22)	10 (6–28)	0.78
Weight gain as % of birth weight at day 28	39 (16–62)	37 (10–59)	0.65
NEC	0/20	1/22	0.76
Time in NICU (days)	22 (6–60)	29 (3–109)	0.20

Data are expressed as median (range).

*Twelve of 24 hours NPO except for the five day test period in both groups and before full feeding.

MEF, Minimal enteral feeding; NEF, no enteral feeding; NPO, nothing by mouth; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit.

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