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

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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 vs 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. Blood flow to heart, brain, and adrenals is increased in compensation, while other organs including the gastrointestinal tract are relatively hypoperfused. Fetal blood flow pulsatility shows this effect by changes in flow velocity waveforms in the cerebral arteries and umbilical arteries. 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. Redistribution of fetal blood flow, also called brain sparing, is characterised by the increase in umbilical artery/middle cerebral artery PI ratio.

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.

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. Studies of MEF in preterm infants have shown varying effects on clinical outcomes such as feeding tolerance and growth.

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. 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. 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...
< 2000 g, and birth weight for gestational age below the
tenth centile,28 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 (Nestle; Nestec, Switzerland
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 digluco-
nate 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 measure-
ment 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 move-
ments). 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.7
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 χ² 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 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 (r² = 0.01, p = 0.55; r² = 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.29 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 al29
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 al29 and Shulman et al30 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.31 In this study, we found a similar
decrease in intestinal permeability to that in our previous
study, 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, length of time feed withheld, time to regain birth weight, and hospital stay. 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. Moreover in this meta-analysis, the possibility that MEF might increase the incidence of NEC could not be excluded. 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. These prenatal haemodynamic disturbances have been associated with increased perinatal mortality and morbidity such as intracranial haemorrhage, infant respiratory distress syndrome, gastrointestinal disturbances, and NEC. However, the study of Mihatsch et al 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 Reuwer). 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. 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**

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**Table 1** Patient characteristics

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

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.

**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)

<table>
<thead>
<tr>
<th></th>
<th>MEF (n = 20)</th>
<th>NEF (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM ratio 1</td>
<td>0.32 (0.02–0.90)</td>
<td>0.26 (0.02–1.1)</td>
</tr>
<tr>
<td>LM ratio 2</td>
<td>0.11 (0.03–0.42)</td>
<td>0.15 (0.00–0.46)</td>
</tr>
<tr>
<td>LM ratio 1–2</td>
<td>0.25 (–0.39–0.62)</td>
<td>0.11 (–0.11–0.84)</td>
</tr>
</tbody>
</table>

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.

1p = 0.14 MEF v NEF.
Table 3  Feeding tolerance and growth

<table>
<thead>
<tr>
<th></th>
<th>MEF (n = 20)</th>
<th>NEF (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to reach full enteral feeding</td>
<td>13 (7–46)</td>
<td>13 (9–23)</td>
<td>0.32</td>
</tr>
<tr>
<td>Days NPO*</td>
<td>0 (0–1.5)</td>
<td>0 (0–3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Days to regain birth weight</td>
<td>11 (5–22)</td>
<td>10 (6–28)</td>
<td>0.78</td>
</tr>
<tr>
<td>Weight gain as % of birth weight at day 28</td>
<td>39 (16–62)</td>
<td>37 (10–59)</td>
<td>0.65</td>
</tr>
<tr>
<td>NEC</td>
<td>0/20</td>
<td>1/22</td>
<td>0.76</td>
</tr>
<tr>
<td>Time in NICU (days)</td>
<td>22 (6–60)</td>
<td>29 (3–109)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). *Two 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.

Authors’ affiliations
M van Elburg, van den Berg, Bunkers, et al

References
