Acta Pædiatrica ISSN 0803-5253

REGULAR ARTICLE

# Near-infrared spectroscopy is a promising noninvasive technique for monitoring the effects of feeding regimens on the cerebral and splanchnic regions

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**Keywords**
Breast milk, Cerebro-splanchnic perfusion, Formula milk, Near-infrared spectroscopy, Preterm infants

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**Received**
28 April 2017; revised 29 June 2017; accepted 22 September 2017.

DOI:10.1111/apa.14099

## ABSTRACT

**Aim:** The effects of different milk and, or, administration regimens on cerebro-splanchnic perfusion are still a matter of debate. We investigated the effects of the bolus administration of breast milk or formula on cerebro-splanchnic oximetry, function and perfusion, assessed by near-infrared spectroscopy (NIRS).

**Methods:** This observational study of 30 infants fed with breast (n = 15) or formula (n = 15) milk, and matched for gestational age and birth weight, was carried out in the neonatal intensive care unit of the C Arrigo Children's Hospital, Alessandria, Italy, a tertiary-level referral centre, from October 2015 to December 2016. NIRS monitoring parameters, such as cerebral and splanchnic oximetry, fraction of tissue oxygen extraction and the cerebral–splanchnic ratio, were recorded before, during and after feeding.

**Results:** Breast milk led to a significant increase in cerebro-splanchnic oximetry and tissue oxygen extraction ($p < 0.001$) during and after feeding, and the cerebro-splanchnic perfusion ratio was significantly higher ($p < 0.001$) in the breast than formula group.

**Conclusion:** Our study results suggest that breast milk was better tolerated than formula, requiring lower energy expenditure and lower cerebro-splanchnic haemodynamic redistribution. The findings could prompt investigations using NIRS as a promising noninvasive tool for cerebral and splanchnic longitudinal monitoring during neonatal feeding.

## INTRODUCTION

The World Health Organization and perinatal networks have established several criteria for excellence in the management of neonatal intensive care units (NICUs), and one of the major issues is ensuring that infants are being fed exclusively with breast milk when they are discharged from hospital (1). Breast milk is now generally recognised to be the best available choice for the nutrition of newborn infants, because of its unique composition of micronutrients and macronutrients (2). This is of particular relevance in the first days of extra-uterine life, when breast milk plays a crucial role in the reformation of the mother–infant dyad (3). Additional advantages of breast milk are complete immune protection, the promotion and development of intestinal motility and microflora and the preservation of barrier integrity (4). In NICUs, breastfed sick infants have been reported to show fewer instances of infection and improved neuro-cognitive development (5), as well as an improved Doppler pattern in splanchnic circulation (6) and near-infrared spectroscopy (NIRS) parameters (7). The existing data support the need for the least invasive possible and accurate monitoring of intestinal development and function. This is especially true for intrauterine growth-

**Abbreviations**

NICU, Neonatal intensive care unit; NIRS, Near-infrared spectroscopy; IUGR, Intrauterine growth-restricted infants; $SO_2$, Oxygen saturation; FTOE, Fractional tissue oxygen extraction; $SaO_2$, Arterial oxygen saturation; SD, Standard deviation.

**Key notes**

- The debate is ongoing about the effects of different milk and, or, administration regimens on cerebro-splanchnic perfusion.
- This was the first study to use near-infrared spectroscopy (NIRS) to show that breast milk was more digestible than formula and required lower energy expenditure and cerebro-splanchnic haemodynamic redistribution.
- The authors concluded that longitudinal NIRS monitoring could provide a promising noninvasive tool for cerebral-splanchnic longitudinal monitoring during neonatal feeding.

 

restricted (IUGR) infants, who are characterised by *in-utero* chronic hypoxia, the brain sparing effect known to be harmful for peripheral organs, especially the gastrointestinal tract (8). In such circumstances, NIRS represents a promising new, noninvasive tool that is able to monitor cerebro-splanchnic oxygenation and function in physiological and pathological conditions (9,10). NIRS parameters, such as regional splanchnic oxygen saturation (regional splanchnic $SO_2$) and fractional tissue oxygenation extraction (FTOE), have been reported to improve during feeding, but this was based on how it was administered, namely bolus versus continuous feeding (7). Adequate cerebro-splanchnic haemodynamic monitoring has also been proposed as way investigating short- and long-term outcomes in IUGR and non-IUGR infants (11,12). It has been reported that regional splanchnic $SO_2$ significantly improved in both healthy and IUGR newborn infants who received bolus rather than feeding, but there were no changes in cerebral oxygenation or function (13). Although oximetry, tissue function and haemodynamic patterns in the cerebro-splanchnic districts of healthy and high-risk infants have been investigated, data comparing breast and formula milk in terms of feeding tolerance are still lacking.

Therefore, this study aimed to investigate whether cerebro-splanchnic oximetry, function and haemodynamic redistribution could change according to different feeding regimens.

## PATIENTS AND METHODS

From October 2015 to December 2016, we conducted an observational study in 30 infants (matched for gestational age and weight at birth admitted to our third-level referral centre for NICU, C. Arrigo Children's Hospital, Alessandria, Italy. Of these, 15 received breast milk and 15 received the same formula milk. Gestational age was determined by clinical data and by longitudinal ultrasound scan monitoring according to the normograms of Campbell and Thomas (14) and by postnatal confirmation in agreement with Bertino et al. (15).

The exclusion criteria were: congenital abnormalities, perinatal asphyxia, the need for cardiovascular support, necrotising enterocolitis, gastrointestinal anomalies and cutaneous diseases impeding the placement of probes. The study protocol was approved by the local ethics committees, and informed consent was provided by the parents of all the patients examined.

The perinatal data, neonatal characteristics and main outcomes are reported in Table 1.

The breast milk and formula milk groups observed the same bolus feeding protocol and were monitored at three time-points: 60 minutes before feeding, 30 minutes after feeding started and 120 minutes after feeding finished. All infants were studied during a full-enteral feeding regimen. No differences were observed between the groups in the duration of feeding ($p < 0.05$) and in the mean volume administrated ($p < 0.05$). Only fresh maternal milk was given to the infants in the breast milk group.

**Table 1** Perinatal characteristics and neonatal outcomes in the breast milk (BM)- and formula milk (MF)-fed groups. Data are given as median ± SD

| | BM (N = 15) | MF (N = 15) | *P* |
|---|---|---|---|
| Maternal characteristics | | | |
| Maternal age (y) | 32 ± 5 | 35 ± 7 | ns |
| Chorioamnionitis (n°/tot) | 0/10 | 0/10 | ns |
| Glucocorticoids (n°/tot) | 7/10 | 7/10 | ns |
| PROM (n°/tot) | 3/10 | 6/10 | ns |
| EPH (n°/tot) | 0/10 | 0/10 | ns |
| Neonatal characteristics | | | |
| GA (wks) | 33 ± 4 | 35 ± 4 | ns |
| BW (g) | 1962 ± 1131 | 2517 ± 834 | ns |
| pH | 7.31 ± 0.10 | 7.32 ± 0.12 | ns |
| CS (n°/tot) | 4/10 | 5/10 | ns |
| Gender (M/F) | 1/9 | 3/7 | ns |
| Outborn/Inborn (n°/tot) | 1/9 | 2/10 | ns |
| Apgar 1′ | 6 ± 1 | 6 ± 2 | ns |
| Apgar 5′ | 8 ± 1 | 8 ± 2 | ns |
| Main outcomes | | | |
| RDS (n°/tot) | 9/10 | 9/10 | ns |
| Surfactant administration (n°/tot) | 5/10 | 4/10 | ns |
| MV (n°/tot) | 10/10 | 9/10 | ns |
| PDA (n°/tot) | 1/10 | 2/10 | ns |
| IVH (n°/tot) | 0/10 | 1/10 | ns |
| EOS (n°/tot) | 0/10 | 3/10 | ns |
| BPD (n°/tot) | 0/10 | 2/10 | ns |
| Monitoring parameters | | | |
| GA (wks) | 36 ± 3 | 37 ± 3 | ns |
| W (g) | 1816 ± 1260 | 2641 ± 582 | ns |
| HR (bpm) | | | |
| RR (breath pm) | | | |
| pH | 7.36 ± 0.03 | 7.37 ± 0.04 | ns |
| Bilirubinemia (mg/dl) | 8.9 ± 1.5 | 9.3 ± 1.2 | ns |
| Hb (g/dl) | 13,1 ± 1.5 | 14.5 ± 2.1 | ns |
| $SaO_2$ at T0 | 98 ± 1 | 98 ± 1 | ns |
| $SaO_2$ at T0 | 98 ± 1 | 98 ± 1 | ns |
| $SaO_2$ at T2 | 99 ± 1 | 99 ± 1 | ns |

BW = Birthweight; BPD = Broncho-pulmonary dysplasia; CS = Caesarean section; EOS = Early-onset sepsis; EPH = Preeclampsia; GA = Gestational age; g = Grams; Hb = Haemoglobin; HR = Heart rate; IVH = Intraventricular haemorrhage; MV = Mechanical ventilation; PDA = Patent ductus arteriosus; PROM = Premature rupture of membranes; RDS = Respiratory distress syndrome; RR = Respiratory rate; $SaO_2$ = Arterial oxygen saturation; W = Weight; wks = Weeks; y = Years; ns = Non significant.

### NIRS monitoring

The NIRS parameters in the cerebro-splanchnic districts were recorded by the Sen Smart X-100 (Nonin Medical, Minnesota, USA). Equanox Advance self-adhesive sensors (Nonin Medical, Minnesota, USA) were placed on the central region of the infants' skulls, and on the infra-umbilical abdomen region. Regional splanchnic $SO_2$ and regional cerebral oxygen saturation (regional cerebral $SO_2$) were calculated by the inbuilt software.

FTOE values in the cerebro-splanchnic districts, namely cerebral FTOE and splanchnic FTOE, were assessed according to the following formula: ($SaO_2$ - regional cerebral $SO_2$)/$SaO_2$.

 

We also calculated the cerebro-splanchnic oxygenation ratio, which is the ratio of cerebral versus splanchnic district oximetry (16), according to the following formula: regional cerebral $SO_2$ divided by regional splanchnic $SO_2$. This ratio has been found to be a valuable index of haemodynamic redistribution in chronic hypoxic infants (17).

**Standard monitoring parameters**

The heart, respiratory rates and arterial oxygen saturation ($SaO_2$) monitoring were continuously recorded by MX700 monitors (Philips, Eindhoven, The Netherlands) at 12-second intervals.

**Statistical analysis**

Perinatal and neonatal characteristics are expressed as means and standard deviations (±SD). The student's *t*-test was used for continuous variables and the two-sided Mann–Whitney *U*-test when parameters were not normally distributed. Comparisons between the different monitoring time-points, before, during and after feeding, were analysed for statistically significant differences by Kruskal–Wallis one-way ANOVA, and multiple comparisons were performed using Dunn's method. Categorical data were analysed by means of Fisher's exact test and Chi-square analysis when appropriate. The statistical significance was set at $p < 0.05$.

## RESULTS

Table 1 shows the perinatal, main outcomes and monitoring parameters in the two groups. No significant ($p > 0.05$) differences were found with regard to maternal age, the incidence of chorioamnionitis, antenatal glucocorticoid administration, premature rupture of membranes or the occurrence of pre-eclampsia. There were no significant ($p > 0.05$) differences between the groups with regard to neonatal characteristics, such as gestational age, weight at birth, arterial cord blood pH, delivery mode, gender, the incidence of outborn and inborn infants and the Apgar scores at one and five minutes. No significant ($p > 0.05$) differences were observed between the groups for the incidence of respiratory distress, surfactant administration, mechanical ventilation support, patent ductus arteriosus, cerebral haemorrhage, early onset sepsis and broncho-pulmonary dysplasia. Indeed, no significant ($p > 0.05$) differences have been found between the groups in gestational age, weight, pH, bilirubinemia, haemoglobin and $SaO_2$ before, during and after feeding time-points.

**NIRS cerebral district patterns**

In the breast milk group, regional cerebral $SO_2$ showed a marked increase in the infants' oximetry, which started before feeding, reached its highest peak during feeding and remained significantly ($p < 0.001$) higher after feeding. Indeed, a significant ($p < 0.001$) difference was also observed during and after feeding. It was notable that when the cerebral FTOE was calculated for the breast milk infants, we observed a significant ($p < 0.001$) progressive decrease during and after feeding, and the cerebral FTOE values during feeding were significantly ($p < 0.001$) higher than after feeding.

In the formula milk group, regional cerebral $SO_2$ showed no significant ($p > 0.05$) differences before and after feeding. Regional cerebral $SO_2$ values after feeding were significantly ($p < 0.001$) lower than those recorded before and during feeding. Of note, when cerebral FTOE was calculated in the milk formula infants, it was significantly ($p < 0.05$) lower during feeding than before feeding. The cerebral FTOE values after feeding were significantly ($p < 0.001$) higher than those recorded before feeding. Moreover, the cerebral FTOE values during feeding were significantly ($p < 0.001$) lower than after feeding.

Figure 1 shows the comparison of regional cerebral $SO_2$ in the breast milk and formula milk groups. No significant ($p > 0.05$) differences were found between groups before feeding, whilst regional cerebral $SO_2$ significantly ($p < 0.001$) differed between the groups when it was recorded during and after feeding. Of note, when cerebral FTOE was compared between groups, we found significantly ($p < 0.001$) higher cerebral FTOE values in the breast milk group during and after feeding (Fig. 1).

**NIRS splanchnic district patterns**

In the breast milk group, regional splanchnic $SO_2$ showed no significant ($p > 0.05$) differences before and during feeding. Lower regional splanchnic $SO_2$ after feeding ($p < 0.001$) than before and during feeding was observed. Of note, when splanchnic FTOE was calculated, breast milk infants showed significantly ($p < 0.001$) increased values during and after than before feeding. Moreover, splanchnic FTOE values during feeding were significantly ($p < 0.001$) lower than after feeding.

In the formula milk group, regional splanchnic $SO_2$ showed no significant ($p > 0.05$) differences before and during feeding, but the values after feeding were significantly ($p < 0.001$) higher than at both of those time-points. Of note, when the splanchnic FTOE was calculated, we observed significantly lower ($p < 0.001$) values in formula milk infants after feeding than before and during feeding. Moreover, the values during feeding were significantly ($p < 0.001$) lower than after feeding.

Figure 2 shows a comparison of regional splanchnic $SO_2$ in the breast milk and formula milk groups. In the formula milk group, these values were significantly ($p < 0.001$) higher during and after feeding than in the breast milk group. Conversely, splanchnic FTOE values in the formula milk group were significantly ($p < 0.001$) lower before and after feeding than in the breast milk group (Fig. 2).

**NIRS cerebral–splanchnic ratio**

In the breast milk group, the cerebro-splanchnic ratio values after feeding were significantly ($p < 0.001$) higher than those recorded before and during feeding, but in the formula milk group, the values after feeding were

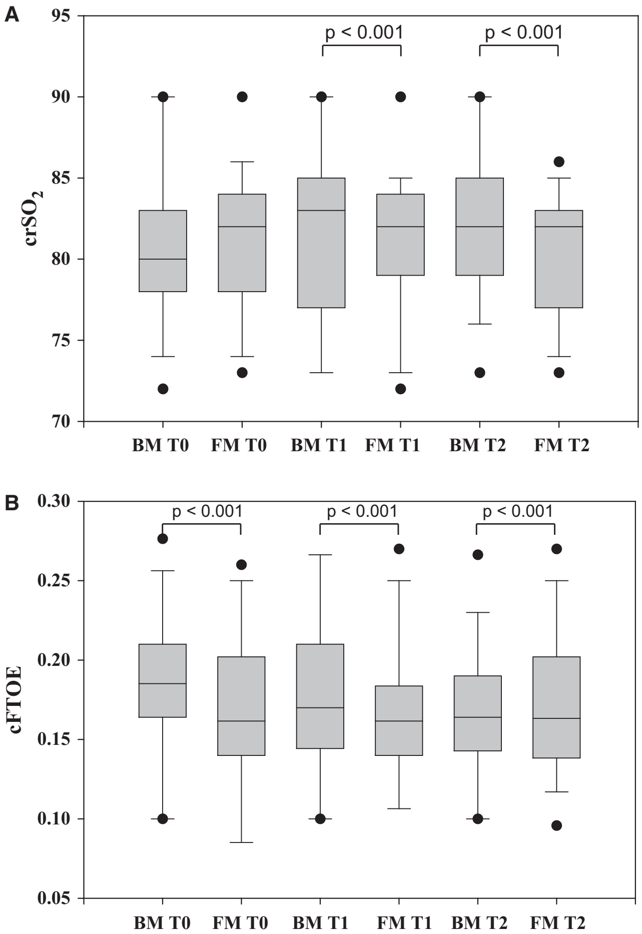


**Figure 1** (A) Regional cerebral oxygen saturation ($crSO_2$) values recorded before (T0), during (T1), after feeding (T2) in breast milk (BM)- and formula milk (FM)-fed infants. Data are given as median and 5-95$^{th}$ centile. (B) Cerebral fractional tissue oxygen extraction (cFTOE) values recorded before (T0), during (T1), after feeding (T2) in breast milk (BM)- and formula milk (FM)-fed infants. Data are given as median and 5-95$^{th}$ centile.

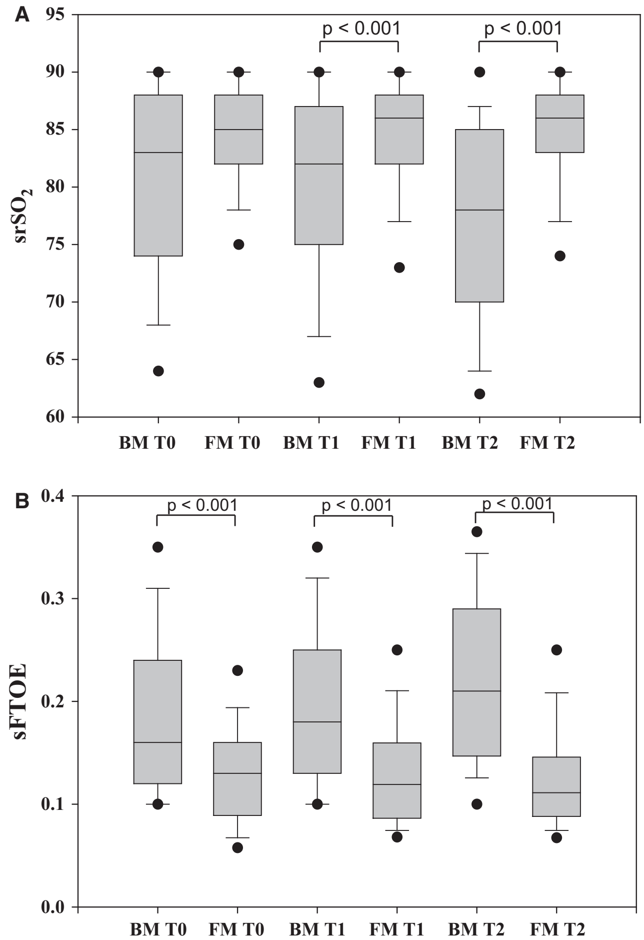


**Figure 2** (A) Regional splanchnic oxygen saturation ($srSO_2$) values recorded before (T0), during (T1), after feeding (T2) in breast milk (BM)- and formula milk (FM)-fed infants. Data are given as median and 5-95° centile. (B) Splanchnic fractional tissue oxygen extraction (sFTOE) values recorded before (T0), during (T1), after feeding (T2) in breast milk (BM)- and formula milk (FM)-fed infants. Data are given as median and 5-95$^{th}$ centile.

significantly ($p < 0.001$) lower than those recorded before and during feeding.

Figure 3 shows a comparison between the cerebro-splanchnic ratio in the breast milk and formula milk groups, and this shows that a significant ($p < 0.001$) increase in the ratio values was observed in the breast milk group during and after feeding.

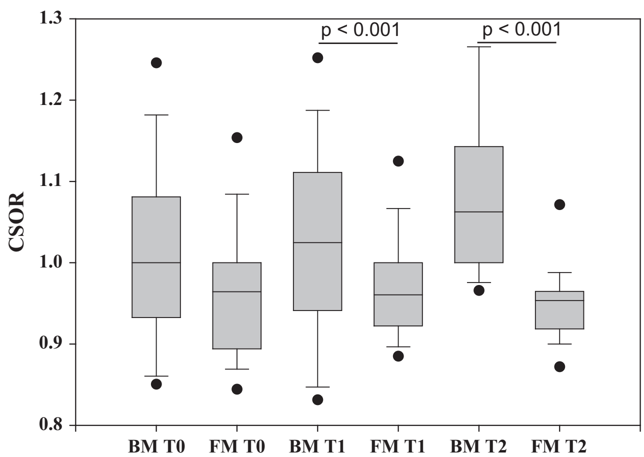


**Figure 3** Cerebro-splanchnic ratio (CSOR), values recorded before (T0), during (T1), after feeding (T2) in breast milk (BM)- and formula milk (FM)-fed infants. Data are given as median and 5-95$^{th}$ centile.

## DISCUSSION

In the present study, we showed that feeding with breast milk significantly improved cerebro-splanchnic oxygenation, function and haemodynamic patterns. Moreover, we found no differences between the groups with regard to clinical and laboratory parameters, such as bilirubinemia, haemoglobin concentrations and arterial oxygen partial pressures, which are known to constitute a potential limitation for NIRS availability.

The NIRS patterns in breast and formula milk-fed infants warrant further consideration. In particular, we found that there were three key results during and after feeding. Firstly, breast milk significantly improved cerebral oxygenation status. Secondly, formula milk caused significant changes in the cerebro-splanchnic oxygenation status, a finding that was also supported by higher splanchnic tissue activation, as shown by lower cerebral FTOE and splanchnic FTOE values. Thirdly, breast milk maintained the cerebro-splanchnic haemodynamic ratio, with a value of more than one, which suggested lower levels of stress in both the brain and the gut.

To our knowledge, this was the first study to compare the effects on cerebro-splanchnic oximetry of breast milk and formula. The differences we observed cannot be attributed to the method of administration, given that both groups were fed with boluses.

The finding of improved cerebral oximetry in the breast milk group during and after feeding deserves further consideration. The discrepancy with previous studies that have reported the absence of any changes in cerebral oximetry may be related to different study designs, especially in terms of monitoring the time-points and duration of NIRS recordings, and the absence of any proper correction for milk products (6,13). It is notable that in formula milk-fed infants, the regional cerebral $SO_2$ pattern showed a significant decrease during and after feeding. We also found a decrease in cerebral FTOE in formula milk-fed infants among the three monitoring intervals, and this parameter was significantly lower than in the breast milk group at all monitoring time-points. The explanation lies in a better activation of cerebrovascular adaptive mechanisms in the breast milk group, to maintain cerebral blood flow and tissue oxygenation and oxygen delivery that was as constant as possible before (digestive stimuli), during and after feeding (18). This finding is also supported by a median cerebro-splanchnic ratio pattern with a value of more than one in the breastfed infants, suggesting a successful adaptation to feeding by the mechanisms responsible for the cerebral auto-regulation system. In contrast, the median cerebro-splanchnic ratio pattern during and after feeding in the formula-fed infants was less than one, reflecting a preferential blood flow distribution to the gut at the expense of the brain. Our data are partially in agreement with those of Bozzetti et al., who found an identical NIRS pattern in IUGR newborn infants monitored in the postnatal transitional phase (17). Altogether and bearing in mind that no differences have been shown in neonatal characteristics, outcome, clinical, laboratory and monitoring parameters before recordings, it is reasonable to argue that infants fed by formula milk have different cerebral oxygenation, function and haemodynamic patterns that are mediated by formula milk. Further studies in wider populations to confirm our observations are justified.

We also found that splanchnic oximetry, function and haemodynamic patterns differed between the breast milk and formula milk groups, with higher regional splanchnic $SO_2$ in the breast milk group and lower splanchnic FTOE and cerebro-splanchnic ratio in the formula milk group. Notably, regional splanchnic $SO_2$ was higher in the formula milk group after feeding than before and during feeding. These findings are partially in agreement with previous observations that reported a significant early increase in splanchnic oxygenation from bolus administration, within 30 minutes (11,13,19). The discrepancy with Corvaglia et al. observations can be attributed to a number of factors: the different study designs, the monitoring time-points and the duration of NIRS recording, the different administration modality, namely bolus versus continuous, and the absence of any proper correction for whether the milk used was breast or formula (13).

The finding of different NIRS parameters in the breast milk and formula milk groups in our study warrants further comment. In particular, higher regional splanchnic $SO_2$ in the formula than breast milk group during and after feeding suggests an increased tissue oximetry at high energy expenditure, which can reasonably be attributed to digestive processes, as supported by higher splanchnic FTOE values. The finding was also corroborated by lower cerebro-splanchnic ratio values in the formula group, which were an expression of a haemodynamic mechanism characterised by a more considerable redistribution of blood flow to the splanchnic district at the expenses of brain and other organs (20). No differences were observed between the groups with regard to perinatal characteristics, clinical or laboratory monitoring parameters at admission and at the monitoring time-points. Based on this, it is reasonable to suppose that the different NIRS patterns were ascribable to the different milks and their by-products, including protein, lipids and glucose, which are characteristics that reasonably require higher tissue energy consumption. In any case, the question of why formula milk appears to be responsible for such metabolic and haemodynamic pattern is a matter of debate that requires further investigation. Speculation that formula milk is less tolerated than breast milk is possible.

This study had a number of limitations. Although the sample size was small, we were able to record a considerable number of NIRS values for each variable at each time-point, with a median of 21,000 values from before to after feeding, thereby reducing the possibility of potential bias. Secondly, a number of technical limitations were commonly encountered during NIRS recordings, particularly fixation problems of the sensors leading to movement artefacts (21). It must be clarified that the reliability of NIRS measurements on the abdomen is still a matter of debate because of the path length of the bowel studied, insufficient infrared light traversing the intestines, gut movements within the abdomen and peristalsis leading to scattering of photons (6,22).

## CONCLUSION

This study provides additional support for the unique properties of breast milk. It also indicates that further investigations using NIRS are useful, and this method is a promising noninvasive way of carrying out longitudinal monitoring of feeding tolerance and its effects on the cerebral and splanchnic regions.

## ACKNOWLEDGEMENTS

This study was part of the IO PhD International Program, under the auspices of the Italian Society of Neonatology.

## FUNDING

This study was partially supported by grants to Diego Gazzolo from the I Colori della Vita Foundation, Italy.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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