# Preterm infant feeding and growth monitoring: Implementation of the INTERGROWTH-21ˢᵗ protocol

## Module 2
## Gastro-Intestinal Development of Preterm Infants

Preterm infant feeding and growth monitoring: Implementation of the INTERGROWTH-21st protocol

OXFORD MATERNAL AND PERINATAL HEALTH INSTITUTE

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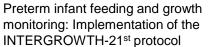Gastro-Intestinal Development of Preterm Infants

## On successful completion of this module you should be able to:

- Understand the rationale for being knowledgeable about the preterm gastro-intestinal system

- Understand the anatomic and physiologic immaturity of the preterm infant and clinical/nutritional implications

- Understand the relevance of necrotising enterocolitis in preterm infants

- Know the physiological differences between amniotic fluid, premature human milk, and term human milk.

- Understand the digestion physiology of protein, lipids and carbohydrates in the preterm infant
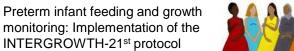
# Gastro-Intestinal Development of Preterm Infants

**Rationale:** Understanding the gastro-intestinal development of the preterm infant is key as it relates to the accretion of nutrients availed to the preterm infant which later determines the rest of physical and neurodevelopment.

The gastro-intestinal system is therefore a 'port of entry' into the overall growth of the preterm infant.

The role of feed intolerance and necrotising enterocolitis (NEC) in preterm infant short and long term growth and development, as well as in survival rates, also justifies focus on this topic".

# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

Development and maturation of the gastro-intestinal system is a continuous process that starts in early fetal life and continues even after term delivery. The gut goes through five phases to reach full maturation:

**Phase 1**- Embryonic phase of organogenesis begins from week 5 of gestation.

**Phase 2**- Formation of rudimentary primitive gut tube and entrance and exit sites of gastro-intestinal tract; fetus starts swallowing amniotic fluid during this phase. Rapid growth with the formation of villi and microvilli.

**Phase 3**- Late gestation. Active differentiation of cells; selective apoptosis at the tips and crypts of villi

**Phase 4**- Begins after birth. Has the largest antigenic load presented to it; differentiates between self and non-self

**Phase 5**- Starts in late infancy during transition from milk to complementary feeds and continues in childhood. Second phase of mucosal expansion renders gut maturity similar to older children

Dasgupta S, Arya S, Choudhary S, Jain SK. Amniotic fluid: Source of trophic factors for the developing intestine. World J Gastrointest Pathophysiol. 2016;7(1):38-47. doi: 10.4291/wjgp.v7.i1.38. Pu
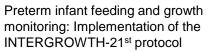
# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

It is clear that preterm gut is presented with the physiologic demand of feeding when the system is immature.

Feed intolerance and necrotising enterocolitis are common findings among preterm infants, and are related to the immature gastro-intestinal system. These conditions often result in parenteral feeding which is associated with complications such as increased chances of sepsis and inflammatory stimuli, gastrointestinal atrophy and thromboses.

It would therefore be incomplete to consider preterm growth monitoring and feeding without understanding the growing gastro-intestinal system of the premature infant and clinical/nutritional implications.

Likewise, awareness of necrotising enterocolitis is key for anyone managing premature infants.
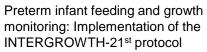
Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(2):629S-34S. PubMed PMID: 17284768.

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# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

**Necrotising Enterocolitis (NEC)**
This is the most common and devastating disease of the gastro-intestinal system of the premature infant, in which the premature gastrointestinal system has increased microbial reactivity. The resulting inflammation leads to mucosal destruction and mesenteric hypoperfusion and eventually necrosis. Resection of the necrosed tissue often leads to short bowel syndrome

While the pathophysiology is more complex than this, three key factors come into play:
❑ Prematurity- incidence varies inversely with gestational age
❑ Bacterial colonization
❑ Type of feeding – mother's own milk exerts a protective role compared to formula

Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. Nat Rev Gastroenterol Hepatol. 2016;13(10):590-600. Epub 2016/08/18. doi: 10.1038/nrgastro.2016.119.
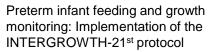
# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

**Necrotising Enterocolitis (NEC)**
Diagnosis

There is an inverse relationship between gestational age and the onset and severity of symptoms. An infant born at ~27 weeks of gestation will typically present with NEC at ~4–5 weeks of age and has a substantially higher risk of NEC development than an infant born at closer to 37 weeks of gestation, for whom onset typically occurs within the first 2 weeks after birth.

The typical neonate with NEC is a premature infant who is thriving, yet suddenly presents with the following gastrointestinal symptoms:
feeding intolerance,
abdominal distension,
bloody stools.

Systemic signs are reflective of the ensuing of sepsis.

Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. Nat Rev Gastroenterol Hepatol. 2016;13(10):590-600. Epub 2016/08/18. doi: 10.1038/nrgastro.2016.119.

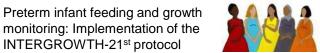# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

**Necrotising Enterocolitis (NEC)**
Diagnosis

Signs of sepsis can be associated with high gastric residuals (defined as the volume that remains in the stomach before the next enteral feeding) of ≥2 ml/kg or >50% of the previous feeding volume, which could indicate the presence of feeding intolerance.

However, use of gastric residuals as an objective measure of NEC is controversial because of inherent variability in sampling gastric contents and lack of standardization in the procedure of obtaining gastric aspirates.

A plain abdominal radiograph reveals intramural gas (pneumatosis intestinalis) in the early stages of confirmed NEC, whereas advanced cases of the disease have pneumoperitoneum.

A full hemogram may reveal neutropenia and thrombocytopenia, although no specific laboratory markers for NEC have been validated.

Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. Nat Rev Gastroenterol Hepatol. 2016;13(10):590-600. Epub 2016/08/18. doi: 10.1038/nrgastro.2016.119.

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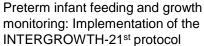
**Necrotising Enterocolitis (NEC)**

NEC in term and late preterm infants seems to have a different pathophysiology, and risk factors in the former largely include those in which intestinal perfusion is compromised, such as low APGAR scores, chorioamnionitis, exchange transfusions, prolonged rupture of membranes, congenital heart disease, and neural tube defects. In this instance, manifestation of NEC is in the early days of life (Claud EC, 2009; Neu J, 2007).

Characteristically occurring between 7-14 days of life, it can still occur several weeks after delivery. The more premature the infant, the later NEC appears to occur (Claud EC, 2009; Neu J, 2007)

Claud EC. Neonatal Necrotizing Enterocolitis -Inflammation and Intestinal Immaturity. Antiinflamm Antiallergy Agents Med Chem. 2009;8(3):248-59. doi: 10.2174/187152309789152020.
Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(2):629S-34S. PubMed PMID: 17284768.

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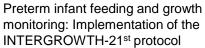
**Anatomic Immaturity**

Preterm delivery suddenly brings to a halt dependence of the fetus on the placenta and amniotic fluid for nutrition and the immature gut of the preterm, which is basically fetal, has to digest and absorb feeds. In addition, enteral feeding means that immunologic, endocrine and exocrine functions have to be summoned earlier than usual.

While intestinal growth almost doubles during the third trimester with an even more dramatic increase in the villi population and hence absorptive surface area, very preterm infants are more likely to miss out on this developmental stage.

Alongside a reduced absorptive capacity, a premature motor function also contributes to food intolerance. An immature enteric nervous system leads to delayed emptying and other than worsening intolerance, the resulting stasis leads to bacterial colonization.

The immature mucosal barrier, innate immunity and increased permeability of the intestinal tract on a background of bacterial overgrowth only facilitates tissue injury.

Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(2):629S-34S. PubMed PMID: 17284768.

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**Physiologic Immaturity**
The lower oesophageal sphincter pressure in the preterm baby is almost a seventh of that in term infants (4 cm H2O vs 28 cm H2O) which is a risk factor for the high incidence of gastroesophageal reflux (GER) in preterm infants (Neu J, 2003).
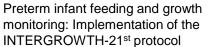
Slower gastric emptying in preterm infants than in their term counterparts also contributes towards GER in the former. Metoclopramide and cisapride increase the gastric emptying rate in both groups. Bypassing the stomach through naso-jejunal feeding may only minimally improve feeding tolerance because the mature migrating myoelectric complexes appear between 33 to 34 weeks' gestation. Before this, the pattern is disorganized (Neu J, 2003).

Gastro-anal transit ranges from 8 to 96 hours in preterm infants compared with 4 to 12 hours in adults. In preterm infants, the motilin receptor is not present until 32 weeks' gestation, and the cyclic release of motilin is not present (Neu J, 2003).

The more preterm a baby is, the greater the delay in passing the first stool (Ayede AI, 2011).

Ayede AI. Achieving optimal feeds for preterm babies, recommendations and realities in practice: nigerian perspective. Ann Ib Postgrad Med. 2011;9(1):1-7.
Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7
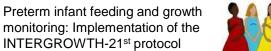
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**Physiologic Immaturity**

Swallowing is a physiological process that starts intra-uterine and amniotic fluid becomes the first meal. The fetus swallows about 250ml/kg/day or a total 450-1000mL/day of amniotic fluid in the third trimester (Dasgupta S, 2016; Neu J 2003).

Replete with amino acids (arginine, glutamine), proteins (lactoferrin), minerals (iron, zinc), amniotic fluid volume is maximum (800ml) at about 28 weeks' gestation  and usually contributes about 15% of the nutritional needs of the fetus (Dasgupta S, 2016; Neu J 2003).

Dasgupta S, Arya S, Choudhary S, Jain SK. Amniotic fluid: Source of trophic factors for the developing intestine. World J Gastrointest Pathophysiol. 2016;7(1):38-47. doi: 10.4291/wjgp.v7.i1.38. Pu

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

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**Physiologic Immaturity**

Apart from nutrition, amniotic fluid also contains hormones (growth hormone; prolactin), growth factors (Insulin like growth factor-1; epidermal growth factor) which are crucial in the maturation of the gut. Trophic effects of amniotic fluid on the gut are comparable to breast milk (Dasgupta S, 2016; Neu J, 2003).

The nutritive and trophic roles of amniotic fluid are interrupted suddenly at the time of preterm birth. It is thought that this sudden interruption of large fluid fluxes from fetal life to extrauterine life might have detrimental consequences (Neu J, 2003)

Subsequently, one of the big questions for future research is the use of synthetic or harvested AF as enteral infusions to promote the development of the GI tract in premature infants or infants recovering from NEC (Dasgupta S, 2016)

Dasgupta S, Arya S, Choudhary S, Jain SK. Amniotic fluid: Source of trophic factors for the developing intestine. World J Gastrointest Pathophysiol. 2016;7(1):38-47. doi: 10.4291/wjgp.v7.i1.38. Pu

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

## Physiological differences: amniotic fluid, "premature" human milk, and "term" human milk

Preterm hindmilk is higher in protein, fatty acids, energy, and fat-soluble vitamins than foremilk.

It also has increased polyunsaturated fats and increased absorption of fat-soluble vitamins. The practice of discarding the foremilk and feeding premature infants predominantly hindmilk has been shown to increase weight gain.

Amniotic fluid contains amino acids, proteins, vitamins, minerals, hormones, and growth factors but in much lower concentrations than in human milk.

However, swallowed amniotic fluid accounts for up to 15% of fetal growth.

Underwood MA. Human milk for the premature infant. Pediatr Clin North Am. 2013 Feb;60(1):189-207.

# Physiological differences: amniotic fluid, "premature" human milk, and "term" human milk

Term and preterm milk differ as follows:

| Component | Preterm Milk | Term Milk |
|---|---|---|
| Protein | Initially higher, decreasing over time | Lower than preterm |
| Fat | Initially higher, decreasing over time | Lower than preterm |
| Free Amino acids | Initially higher, decreasing over time | Lower than preterm |
| Sodium | Initially higher, decreasing over time | Lower than preterm |
| Calcium | Lower, with no increase over time | Higher |
| Copper and Zinc | Higher | Lower |

Underwood MA. Human milk for the premature infant. Pediatr Clin North Am. 2013 Feb;60(1):189-207.
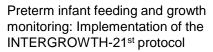
## Physiological differences: amniotic fluid, "premature" human milk, and "term" human milk

Other bioactive molecules are also important in the innate immunity of breast milk. These include: cytokines, growth factors, and lactoferrin which are higher in preterm than term milk.

Leptin is produced by mammary glands, secreted into human milk, and may be important in postnatal growth. Concentrations do not seem to differ between preterm and term milk.

Bile salt stimulated lipase activity is similar in term and preterm milk, whereas lipoprotein lipase activity is higher in term milk.

Underwood MA. Human milk for the premature infant. Pediatr Clin North Am. 2013 Feb;60(1):189-207.

## Physiological differences: amniotic fluid, "premature" human milk, and "term" human milk

Lactose is the most abundant carbohydrate in breast milk and the largest source of energy (Underwood MA, 2013).

In preterm milk, lactose concentrations are lower than in term milk and this might have positive effects in preterm nutrition, because it contributes to lower milk osmolality. Low levels also might represent lower substrate levels for the well-known lactase deficiency that is common among such newborns (Gabrielli O, 2011).

Complex oligosaccharides, otherwise known as human milk oligosaccharides (HMO) are second in abundance. Indigestible by human glycosidases, they have three major roles (Underwood MA, 2013):

- Prebiotic (stimulation of commensal bacteria containing the bacterial glycosidases to deconstruct and consume the HMOs)
- Decoy (structural similarity to the glycans on enterocytes allows HMOs to competitively bind to pathogens)
- Provision of fucose and sialic acid, which seem to be important in host defence and neurodevelopment, respectively.

Gabrielli O, Zampini L, Galeazzi T, Padella L, Santoro L, Peila C, Giuliani F, Bertino E, Fabris C and Coppa G. Preterm milk oligosaccharides during the first month of lactation. Pediatrics 2011;128:1520-31
Underwood MA. Human milk for the premature infant. Pediatr Clin North Am. 2013 Feb;60(1):189-207.
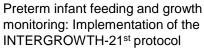
## Physiological differences: amniotic fluid, "premature" human milk, and "term" human milk

HMOs are present in higher concentrations in preterm milk compared with term milk and this aspect highlights the relevant role of breastfeeding for preterm infants, who, because of the immaturity of their organs and systems, are at greater risk of contracting various illnesses, particularly infectious illnesses (Gabrielli O, 2011).

The different HMO concentrations in preterm and term milk might simply reflect aging of the cells responsible for milk secretion, or they might represent a programmed adaptation of milk composition to the specific needs of the infants (Gabrielli O, 2011).

Glycosaminoglycans are polysaccharides that act as decoys, providing binding sites for pathogenic bacteria to prevent adherence to the enterocyte. Premature milk is richer in glycosaminoglycans than term milk (Underwood MA, 2013).

Gabrielli O, Zampini L, Galeazzi T, Padella L, Santoro L, Peila C, Giuliani F, Bertino E, Fabris C and Coppa G. Preterm milk oligosaccharides during the first month of lactation. Pediatrics 2011;128:1520-31.

Underwood MA. Human milk for the premature infant. Pediatr Clin North Am. 2013 Feb;60(1):189-207.

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# The Immature Gastro-Intestinal System of the Preterm Infant and Clinical Implications

**Physiologic Immaturity**

Protein digestion

The protein content of preterm milk is higher than term milk (see section on breastfeeding) (Neu J 2003; Dallas DC 2012). Human milk also contains several proteases such as plasmin, whose concentration is higher in preterm than term breast milk. The protease levels seem to decrease with the infant's increasing protein-degradative capacity but their activity within the breast is balanced by antiproteases (Dallas DC, 2012).

Once milk is transferred from the breast to the infant, digestion naturally starts in the oral cavity but in preterm infants, gavage feeding due to a poorly coordinated swallow-breathe cycle, occludes contact between milk proteins and potential proteases/antiproteases in the mouth, other than through swallowed saliva (Dallas DC, 2012).

Dallas DC, Underwood MA, Zivkovic AM, German JB. Digestion of Protein in Premature and Term Infants. J Nutr Disord Ther. 2012;2(3):112. doi: 10.4172/2161-0509.1000112.

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

# The Immature Gastro-Intestinal System of the Preterm Infant and Clinical Implications
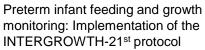
**Physiologic Immaturity**

Protein digestion

Gastric proteolysis is favoured by a highly acidic pH. Gastric acid, important in protein denaturation which facilitates further proteolysis, and acting as a barrier against micro-organisms, doubles between the first and fourth postnatal week in preterm infants in relation to the increasing parietal cell mass, which increases with growth. Production is also influenced by feeding regimen (Neu J 2003; Dallas DC, 2012).

However, premature infants produce less feeding-stimulated gastric acid than term infants, a difference that disappears by the end of the fourth postnatal week. Moreover, breast milk (pH 7.0-7.6), has a buffering effect maintaining gastric pH close to non-denaturing neutral levels. As such, premature infants have a post-prandial gastric pH of 5–7 for up to an hour which drops to pH 3–3.5 three hours postprandial (Neu J 2003; Dallas DC, 2012).

Use of H2 blockers has the detrimental effect of promoting micro-organism colonization of the distal gastro–intestinal tract (Neu J 2003).

Dallas DC, Underwood MA, Zivkovic AM, German JB. Digestion of Protein in Premature and Term Infants. J Nutr Disord Ther. 2012;2(3):112. doi: 10.4172/2161-0509.1000112

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

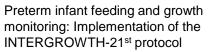**Physiologic Immaturity**

Protein digestion

Proteolytic activity of some enzymes is also influenced by gastric pH. Pepsin optimally hydrolyses protein at acidic pH.

Other enzymes or zymogens necessary in protein digestion such a pepsin, trypsinogen and enterokinase are also lower in preterm infants. For example, pepsin secretion is fully developed by 3 to 8 months postnatally, and the much lower levels in preterm infants limit protein digestion (Neu J 2003).

Luminal digestion is facilitated by many other proteolytic agents. In one study, enterokinase activity, necessary for the conversion of trypsinogen to trypsin which in turn converts other zymogens to active agents, was 6% and 20% at 26–30 weeks' gestational age in premature and term infants, respectively (Dallas DC, 2012).

Dallas DC, Underwood MA, Zivkovic AM, German JB. Digestion of Protein in Premature and Term Infants. J Nutr Disord Ther. 2012;2(3):112. doi: 10.4172/2161-0509.1000112.

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

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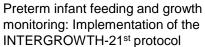
**Physiologic Immaturity**

Lipid digestion

Lipids make up about 50% of the nonprotein energy content of human milk and formula (Neu J, 2003).

Intrauterine fat deposition occurs in the last trimester; thus, the preterm infant is deficient in fat which is necessary for energy and thermogenesis (Ayede AI, 2011). Lipids also play an important role in neurodevelopment especially Docosahexaenoic acid(DHA) and arachidonic acid (Neu J, 2003).

Maturation of the digestive system (digestive function i.e., enzyme and bile salt levels, absorptive capacity, or a combination of both) determines the proportion of lipids absorbed. It is estimated that term infants excrete approximately 10% fat in stools whereas preterm infants excrete approximately 10-30%. The amount of unabsorbed fat appears to depend essentially on gestational and postnatal age and the type of fat (Abrahamse E, 2012).

Abrahamse E, Minekus M, van Aken GA, van de Heijning B, Knol J, Bartke N, et al. Development of the Digestive System-Experimental Challenges and Approaches of Infant Lipid Digestion. Food Dig. 2012;3(1-3):63-77. Epub 2012/11/07. doi: 10.1007/s13228-012-0025-x.

Ayede AI. Achieving optimal feeds for preterm babies, recommendations and realities in practice: nigerian perspective. Ann Ib Postgrad Med. 2011;9(1):1-7.

Neu J and Li N. The Neonatal Gastrointestinal Tract: Developmental Anatomy, Physiology, and Clinical Implications. NeoReviews 2003;4;7 DOI: 10.1542/neo.4-1-e7

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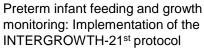
**Physiologic Immaturity**

## Lipid digestion

Several lipases are involved in the hydrolysis of fats which include lingual, gastric, pancreatic, epithelial lipases and the lipase found in human milk (bile salt-stimulated lipase). Bile acid-stimulated lipase is activated in the intestinal lumen in the presence of bile acids. Unlike older children, both term and preterm infants have pancreatic insufficiency, hence decreased levels of pancreatic lipase, which will have implications for digestion of lipids (Neu J, 2003).

Interestingly, despite the low levels of bile salts and pancreatic lipase in newborns, fat intake in newborns (2.5–3.5 g/kg birth weight/day) is three to five times higher compared to adults. In essence, several mechanisms seem to compensate for this relative immaturity of the pancreatic, intestinal, and hepatobiliary systems in the term infant (Abrahamse E, 2012).

However, absorption of other lipid-soluble substances, such as cholesterol, and fat-soluble vitamins (A, D, E, K) are almost completely dependent on the presence of bile (Abrahamse E, 2012).

Abrahamse E, Minekus M, van Aken GA, van de Heijning B, Knol J, Bartke N, et al. Development of the Digestive System-Experimental Challenges and Approaches of Infant Lipid Digestion. Food Dig. 2012;3(1-3):63-77. Epub 2012/11/07. doi: 10.1007/s13228-012-0025-x.
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# Understanding the Immature Gastro-Intestinal System of the Preterm Infant

**Physiologic Immaturity**

Carbohydrate digestion

Lactose is the major carbohydrate in human milk. An important energy source, it is relatively low in colostrum, and increases over time with more dramatic increases in preterm milk (see above) (Underwood MA, 2013).

While sucrase, maltase, and isomaltase are usually fully active in the preterm infant, lactase activity, which increases markedly from 24 to 40 weeks' gestation, may be low (Neu J, 2003).
This lactase activity in the preterm less than 34 weeks' gestation has about 30% of the activity seen in term babies (Ayede AI, 2011).

Subsequently, lactase activity is a marker of intestinal maturity and may influence clinical outcomes. Early feeding has been shown to increase intestinal lactase activity in preterm infants (Neu J, 2003).

Despite these developmental patterns, clinical lactose intolerance is uncommon. Postnatal adaptive responses to ingested carbohydrates combined with fermentation by colonic flora improves absorption (Neu J, 2003).

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## You have completed the module Understanding the Immature Gastro-Intestinal System of the Preterm Infant and you should now be able to:

- Understand the anatomic differences between a preterm and term gastro-intestinal system

- Understand the physiologic differences between a preterm and term gastro-intestinal system

- Describe and possibly identify necrotising enterocolitis

- Identify differences between amniotic fluid, preterm and term human breast milk

- Describe the digestion of protein, lipids and carbohydrates in preterm infants

Preterm infant feeding and growth monitoring: Implementation of the INTERGROWTH-21st protocol

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Module 2: Gastro-Intestinal Development of Preterm Infants

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