CURRENT TOPIC

Gastric ontogeny: clinical implications

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The delivery of a preterm infant offers a unique opportunity to look directly upon the process of ontogeny, while at the same time organ immaturity is the basis of the clinical problems which challenge neonatal medicine. In recent years our knowledge of foregut ontogeny has increased, together with an increased body of clinical experience, yet the nutritional management of the preterm infant remains a contentious area, with wide variations in clinical practice. The compelling evidence of the importance of early nutritional management on neurodevelopmental outcome now focuses the debate sharply. Closer knowledge of the development of functional maturity in the gut may allow more rapid and rational advances to be made. In this paper we discuss the embryology, the development of secretory and digestive function, and the maturation of gastro-oesophageal motor activity as a background to the clinical management of nutrition in the preterm infant.

General embryology

The human stomach develops from a fusiform swelling of the foregut at about 4 weeks' gestation. Originating in the neck, this swelling descends into the abdomen during the next eight weeks. Differential growth rates result initially in the formation of the greater and lesser curvatures, followed by a 90° clockwise rotation of the stomach which occurs at 6 weeks' gestation.¹ The stomach is initially lined by stratified² or pseudostratified³ columnar epithelial cells which are later replaced by cuboidal cells. Gastric pits have developed in the epithelium by 14 weeks' gestation, and develop a mature glandular structure over the following weeks. Structural maturity is reached before the fetus becomes viable, and by 20 weeks' gestation the fetal stomach macroscopically and microscopically resembles that of the newborn infant at term.

Nerve fibres reach the gastric primordium at 5 weeks' gestation, four weeks before the first myoblasts are seen, and by 30 weeks' gestation both are morphologically and histologically mature.^{4 5}

Acid secretion

Gastric acid has many important functions in the human, including a role in the luminal immune system and the initiation of digestion. Hydrogen ions are secreted by the parietal cells

located on the luminal aspect of the gastric mucosa by an energy dependent H^+/K^+ ATPase (proton pump). Acid secretion is under neural and hormonal control, principally vagal stimulation and local secretion of gastrin and histamine. These act either directly on the parietal cell or through enterochromaffin-like cells.

Differentiated glandular epithelial cells, which are structurally and histochemically identifiable as parietal cells, appear from 11 weeks' gestation.⁶ During early fetal life parietal cells are located in the body and antrum of the stomach, but by term only 20% of neonates have parietal cells in the antrum, similar to the proportion seen in adults.⁷ We have shown that from 13 weeks' gestation these parietal cells are functionally mature with the H^+/K^+ ATPase *in situ*,⁸ and as early as 1929 Lucas-Keene and Hewer found hydrochloric acid in the fetal stomach from 19 weeks' gestation.⁹ It is not known how much acid the fetus produces *in utero* but we have recently demonstrated the secretion of gastric acid in even the most immature infants, from 24 weeks' gestation. In this study infants receiving intensive care were all found to be capable of producing and maintaining a gastric pH <2 within the first days of life.¹⁰ The principal mechanisms controlling acid secretion in the preterm infant and the effects of factors such as enteral feeds are not known.

Gastric acid has both beneficial and detrimental effects in the immature newborn infant. Its presence acts as a barrier to the entry of micro-organisms into the small intestine, and one study has shown that infants given cimetidine had a higher incidence of necrotising enterocolitis than a control group.¹¹ Gastric acid may therefore have a role in controlling gut microflora implicated in the aetiology of necrotising enterocolitis.

On the other hand, acid related disease may occur. Acid and pepsin are both present in the newborn,¹² and mucosal damage occurs when there is imbalance between their harmful effects and mucosal protective mechanisms. Protection against acid-peptic damage is provided by a number of factors. It requires good gastric mucosal perfusion from the splanchnic circulation. Prostaglandins, notably PGE_2 which is present in the gastric juice of sick preterm infants,¹³ have a number of actions which suggest their central role in mucosal protection. They stimulate mucus production and secretion of bicarbonate,

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inhibit acid secretion, and increase mucosal surface hydrophobicity. Epidermal growth factor (EGF) may also be cytoprotective. This acid stable peptide, present in large amounts in breast milk,¹⁴ produces inhibition of acid secretion in experimental animals.¹⁵ Receptors for EGF have now been demonstrated in the gastric mucosa of the fetus and the newborn.¹⁶

The preterm neonate is at high risk of acid-peptic disease. Sick preterm infants have been demonstrated to have a lower gastric pH than other preterm infants, increasing the risk of gastric bleeding.¹⁷ Mucosal resistance to acid peptic digestion may be reduced by poor gastric blood flow. Dexamethasone and indomethacin inhibit the production of cytoprotective prostaglandins, and tolazoline and morphine increase histamine concentrations. It is therefore not surprising that studies using endoscopy suggest a high incidence of mucosal lesions.¹⁸ Acid-peptic disease is most frequently restricted to superficial mucosal damage, but may produce more significant ulceration or haemorrhage. Gastric perforation is a rare but catastrophic event in sick, stressed, preterm infants, and carries a 50% mortality. It has been described in the fetus.¹⁹ In the neonate it may occur in association with dexamethasone²⁰ and tolazoline²¹ treatment and there is a worrying theoretical risk with morphine.²²

What strategy might therefore be adopted to best protect the preterm infant from acid-peptic disease? Circulatory support to avoid gastric hypoperfusion, and judicious use of agents likely to reduce mucosal resistance is prudent. When upper gastrointestinal bleeding occurs, or when the risk is high, as with the use of high dose dexamethasone, therapeutic or prophylactic intervention is justified. Milk feeds increase gastric pH. In healthy preterm infants receiving three hourly formula feeds, buffering of intragastric pH >4 lasts up to 90 minutes after a feed,²³ and breast milk containing EGF, may confer further benefit. The histamine antagonist, ranitidine, is effective in the preterm infant. Intragastric acidity may be reduced to pH >4, a value thought to prevent acid-peptic disease, with an intravenous infusion of ranitidine at 0.0625 mg/kg/hour.²⁴ The efficacy of H₂ blockade in the prevention of mucosal lesions requires a controlled trial in the intensive care population. There are no data concerning omeprazole in the preterm infant. Sucralfate, which adheres to damaged mucous membrane and promotes local prostaglandin and mucus production, is effective in stress ulceration in adults, but may retard gastric emptying and has been reported to cause bezoar formation in a low birthweight infant.²⁵ Misoprostol, a prostaglandin analogue, may have beneficial effects through reversal of the steroid induced disruption of cytoprotective mechanisms. Experience with misoprostol in the newborn is small, and long term use of prostaglandins to maintain patency of the ductus arteriosus in infants with congenital heart disease has been associated with gastric outlet obstruction.²⁶

GASTRIN

Gastrin is produced by G cells found within the antrum, pylorus, and duodenum. It is both a trophic hormone and a potent stimulant of gastric acid secretion. Immunohistochemical studies have demonstrated small numbers of G cells between 12 and 18 weeks' gestation,²⁷ becoming more numerous in the antrum as the density of parietal cells decreases.⁸ The mechanism linking gastrin and acid production in newborns is not understood but is thought to be different from that in adults. Newborn infants have significantly higher circulating concentrations of gastrin than adults, these high concentrations persist until at least 4 months of age. Under 3 months of age infants do not demonstrate the typical postprandial rise in gastrin seen in adults,²⁸ and administration of the synthetic analogue pentagastrin produces no increase in gastric acid production.²⁹ It is likely therefore that in the newborn, gastrin activity is maintained at maximal level.

Motility

Gastric and oesophageal motility are integrally linked, and it is worth noting the ontogenic coincidence of swallowing and mature lower oesophageal sphincter (LOS) function and small intestinal motility.

OESOPHAGUS

Interest here centres on the complex integrated function of swallowing and the lower oesophageal sphincter as a barrier against gastro-oesophageal reflux (GOR). Swallowing is first seen from 12–16 weeks, and has an important role in the regulation of liquor volume, as the fetus swallows 2–7 ml/day initially, rising to 300–700 ml/day at term.³⁰ The role of swallowed liquor in the gastrointestinal ontogeny is not clear. Liquor is known to contain proteins, carbohydrates, and triglycerides which may be important as luminal nutrients. It clearly provides volume which may encourage the maturation of motility through secretion of enteric hormones,³¹ and interest recently has focused upon the large amount of growth factors present in the amniotic fluid.³² EGF, probably originating from the amniotic membranes, is present in high concentrations in liquor.¹⁶ In murine models, the administration of EGF antisera to the newborn is associated with significant retardation of small intestinal growth and maturity.³³

Swallowing is a complex function, integrating the movement of a bolus from the mouth to the stomach with protection of the airway, inhibition of respiration, and appropriate relaxation of the oesophageal sphincters and the gastric fundus. In the newborn, non-nutritive sucking may be seen at a very early gestation but nutritive sucking and swallowing does not occur until 34 weeks' postconceptional age, even if infants are born earlier and have received intragastric milk feeds. This is unlike some other features of gut ontogeny,

such as small intestinal motility which is increased when milk feeds are given, although mature patterns are not seen before 32 weeks.³⁴

Little is known of the function of the upper oesophageal sphincter which may be detected manometrically from 32 weeks' gestation, 6–8 cm from the nares, and which shows the same response to a dry swallow in low birthweight and term infants.³⁵ Coordinated motor activity in the body of the oesophagus is not present in the preterm,³⁵ showing some of the features seen in older children with GOR.³⁶ Oesophageal peristalsis matures with postnatal age and exposure to milk feeds.³⁵

The LOS is the principal antireflux barrier.³⁷ An effective LOS pressure must exceed intra-abdominal pressure in the fundus of the stomach. In the adult anatomical studies have now demonstrated the muscular equivalent of the high pressure zone,³⁸ although the mechanisms of neuronal and hormonal control remain elusive. In the opossum, which is very immature at birth, an effective LOS pressure is present at birth, with continued maturation of muscle mass and function in the postnatal period.³⁹ Similar observations have been made in the cat and dog.⁴⁰

Studies in the human infant require careful attention to the physics of intraluminal pressure measurement which requires a continuously perfused, rapid response, low compliance manometric system.⁴¹ Details of system design were not given in a study which showed the absence of any effective sphincter pressure in the first six weeks of life in term or preterm infants.⁴² Newborn infants, however, do not reflux continuously, and a study of term infants at a mean age of 8 hours demonstrated effective LOS pressure equal or greater than those seen in older children.⁴³ In the preterm infant effective LOS pressures rises from around 0.53 kPa (4 mm Hg) before 28 weeks to 2.40 kPa (18 mm Hg) at term. This rise in pressure is most clearly related to gestation at birth and postconceptional age rather than postnatal age or postnatal experience.⁴⁴

GASTRO-OESOPHAGEAL REFLUX

GOR occurs when the LOS fails to prevent it. There is, however, no clear relationship between resting LOS pressure and GOR in the individual.^{45–46} This apparent paradox may be explained by motility studies. Reflux may occur in subjects with low sphincter pressure in association with a rise in intra-abdominal pressure. Alternatively it is seen during transient relaxation of the LOS, appropriately after a swallow, or inappropriately at other times.⁴⁷ Similarly studies relating GOR to gastric emptying (see below) are at variance. It seems likely that the individual with good LOS function and rapid gastric emptying will be at low risk of GOR, while when either of these mechanisms is deficient, as occurs in the preterm infant, the risk of GOR will be increased.

In the preterm infant the combined effect

of a poor antireflux barrier, immature oesophageal motility, and slow gastric emptying, make the risk of GOR high. Among preterm infants who have no symptoms to suggest reflux, 85% have a reflux index (percentage exposure time of the oesophagus to a pH <4) greater than 1%, with a mean reflux index of 4.5%.⁴⁶ This is higher than seen in healthy term infant.⁴⁸ Caffeine, which reduces LOS pressure, and physiotherapy, which increases intra-abdominal pressure, are both associated with increased reflux,⁴⁶ while mechanical ventilation, which maintains a positive intrathoracic pressure, is associated with a diminution in the amount of reflux.^{49–50} There is now little doubt that reflux may be implicated in the pathogenesis of the problems of recurrent apnoea,⁴⁶ bronchopulmonary dysplasia,⁵¹ aspiration pneumonitis,⁵² and oesophagitis,⁵³ and these issues have been discussed in detail elsewhere.

GASTRIC EMPTYING

In the active fetus between 26 weeks' gestation and term, liquor fills and empties from the stomach with a periodicity of around 45 minutes.⁵⁴ In the early postnatal period adequate gastric emptying is essential for the introduction of enteral nutrition, and poor gastric emptying is common in the preterm infant, presenting as failure to 'tolerate' milk feeds. In the very low birthweight infant this problem may resolve quickly and spontaneously but may be protracted, and yet little is known about gastric emptying in these infants because of the methodological difficulties of studying small volume feeds, in infants receiving intensive care.⁵⁵

Manometric studies in the preterm infant have shown poorly organised, non-rhythmic gastric pressure waves following on from oesophageal peristalsis.³⁵ Pressure in the fundus⁴⁴ and antrum³⁴ rises with increasing postconceptional age. Gastric emptying has been measured in the preterm infant established on milk feeds. Half emptying times for breast milk have been estimated between 20 and 40 minutes.^{55–57} This is slower than the term infant and follows a biphasic curve, with an initial fast phase which is less obvious when artificial formula is used.⁵⁶ A number of factors have been shown to have an effect upon gastric emptying. The stomach empties less quickly with increasing energy density,⁵⁸ higher fat and long chain triglyceride content,⁵⁹ and greater dextrose concentration,⁶⁰ and is modified by position and postnatal disease.⁶¹ Emptying is more rapid when breast milk is used rather than formula,^{56–57} glucose polymers rather than dextrose, and medium chain rather than long chain triglycerides.⁵⁹ Osmolality,⁶² temperature of the feed, phototherapy,⁶³ and non-nutritive sucking⁶⁴ have been studied without an apparent affect upon emptying.

If the relationship between gastric emptying and gestation or the effects of early introduction of milk feeds are to be explored a technique capable of repeated measurements of emptying of small volume feeds without

disturbance of the infant in intensive care is required. Radiographic and isotope techniques have obvious drawbacks. Measurement of residual volume can only be done once during each feed and assumes that the stomach can be emptied through an intragastric tube. Dye dilution techniques have been refined and allow accurate repeated measurement of intragastric volume.⁶⁴ Dye, however, must be instilled and mixed with gastric contents making this technique less suitable for the study of small volume feeds. We have recently used ultrasound to make repeated assessments of antral cross sectional area during a feed,⁵⁵ allowing the study of feeds down to 4 ml volume, with minimal disturbance to the infant. This method has been used to demonstrate marked difference in gastric emptying of breast milk and formula.⁵⁷

Future work will need to look at the effects of maturity, postnatal age, and the effects of feeding upon gastric emptying. Current knowledge concerning the physiological control of the maturation of gastric emptying is poor, and the relationship between GOR and gastric emptying needs elucidation as the current evidence in this area is conflicting. The modulation of gastric emptying through refinements of the composition of milk and timing and method of feed administration requires exploration. Cisapride, a prokinetic agent, has been used in infants in a dose range of 0.1–0.3 mg/kg/dose, eight hourly, to accelerate gastric emptying and for the control of GOR. One uncontrolled study in preterm infants has demonstrated improved gastric emptying,⁶⁵ but double blind controlled studies are needed to determine its potentially beneficial role.

In the term infant, persistent clinical problems as a result of poor gastric emptying are rare. Infants with congenital gut anomalies, notably gastroschisis, on the other hand may have protracted problems. The origin of these problems is unclear. It may relate to the abnormal intrauterine environment of the gut, or perinatal and postnatal trauma. The association between chronic intestinal pseudo-obstruction and the persistence of motility disorders in infants who have had malrotation may allow inference of a primary motility disorder which may have led to the congenital abnormality.⁶⁶

Digestive functions

Digestion is initiated within the stomach, with the secretion of both acid and pepsin. A variety of pepsins are released in response to antral distension through complex neural and hormonal mechanisms. Pepsinogens have been demonstrated immunohistochemically, in the chief cells from 19–21 weeks' gestation,⁶⁷ and peptic activity is present in the stomach in the very low birthweight infant.⁶⁸ Jejunal feeding, however, is associated with normal gastrointestinal absorption and function,⁶⁹ and the contribution of peptic activity to protein digestion may be small.

The initial hydrolysis of dietary triglycerides

begins in the stomach through the action of acid stable lipase. Gastric lipase appears from the 11th week of development and is secreted in the fundal region of the stomach.⁷⁰ Acid stable lipase activity is of gastric origin, although the part played by lingual and breast milk lipases in initial digestion is unknown. Amniotic fluid contains triglycerides (120 mg/l),⁷¹ and gastric digestion of lipids may begin during fetal life. In a study of 350 preterm infants lipolytic activity in gastric aspirates was found to reach peak activity at 30–32 weeks' gestation.⁷²

INTRINSIC FACTOR

Intrinsic factor is a small glycoprotein synthesised and secreted by the parietal cells under the same neural and hormonal mechanisms involved in modulating acid secretion. It binds to the cobalamin present in vitamin B-12 and is absorbed intact in the terminal ileum. Immunohistochemical⁸ and autoradiographic⁷³ techniques have noted that intrinsic factor is present in parietal cells from the end of the first trimester. There are no clinical studies looking at the secretion of intrinsic factor or absorption of vitamin B-12 in the immature infant.

Conclusion

The upper gut shows considerable structural and functional maturity by the end of the second trimester, but problems related to its function are common in the very low birth-weight infant. Awareness of prenatal factors, the influence of intrauterine nutrition, and of elements of postnatal care that may affect gastrointestinal ontogeny is essential for future advances in the use of enteral feeding. The observation that LOS maturation is not modified by postnatal factors, while gastric emptying clearly is, is hard to explain. Our ability to induce gut maturity and the use of milk feeds, not only as a source of nutrition, but also as a method of promoting maturation, needs further exploration.

Gastric acid is produced by the preterm infant and endoscopy is beginning to provide data which suggest that we may have been under-recognising acid-peptic disease. However, there is insufficient evidence to support the suggestion that all undergoing intensive care should receive acid blocking agents. Currently reduction of gastric acid production may be justified in infants at high risk of acid-peptic mucosal damage. H₂ blockade with ranitidine is effective in increasing gastric pH, but omeprazole or cytoprotective prostaglandin analogues may be used in the future.

Poor LOS function, slow gastric emptying, and immature patterns of gastro-oesophageal motility make GOR common. The role of GOR in the pathogenesis of respiratory problems is now well established. GOR has a natural history of resolution in most infants, but when necessary, treatment may be effective, and will probably increasingly

include the use of cisapride. Slow gastric emptying may increase reflux, but most frequently presents with poor 'toleration' of feeds. Studies involving manipulation of feed composition and timing may well be helpful in these infants, allowing better prediction of a baby's ability to tolerate feeds, and providing guidance in the choice of milk and mode of administration. The study of gastric emptying exemplifies well how research into the natural history of ontogeny, and the effects of intrauterine and postnatal environment upon that process, may, in the future, allow the formation of a rational basis for the nutritional management of the preterm infant.

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