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Ontogeny of fasting small intestinal motor activity in the human infant

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SUMMARY **A clearly defined progression of fasting small intestinal motor development is seen in the human infant from disorganised low amplitude motor activity before 31 weeks gestation through an intermediate phase of increasing motor organisation and amplitude to the development of a normal cyclical pattern of motor activity with clearly defined phase I, II, and III activity between 37 weeks gestation and term. With increasing maturity smooth muscle contractility [gastric antral pressure (5–30 mmHg), average duodenal pressure (2–12 mmHg)], propagation and slow wave frequency (10·5–12·5 cpm) all increased in a significant fashion ($p<0·01$). The stage of development of fasting motor activity in the small intestine of the preterm infant can now be readily predicted from the gestational age of the infant.**

The survival of the preterm infant is dependent on its ability to successfully adapt from intra to extrauterine life. With improvement in the management of initial respiratory conditions, more very premature infants are surviving, but their continued survival depends upon the ability of the gastrointestinal tract, particularly the small intestine, to allow adequate nutrition. Human fetal small intestinal absorptive and brush border digestive function is relatively advanced by the third trimester of pregnancy[1,2] but motor activity is by comparison somewhat retarded.[3] As efficient small intestinal function requires the integration of digestive, absorptive, and motor function, the relative immaturity of motor function in the premature infant may be a major limiting factor in the tolerance of feeds.

The tissues of the alimentary tract differentiate and mature in a species dependent pattern which is determined by genetic, environmental, and species specific endogenous regulatory mechanisms. Knowledge regarding the ontogeny of intestinal motor activity in the human is scanty. Using amniography McLain[3] showed that there was little or no movement of contrast along the fetal gut before 30 weeks gestation and thereafter there was increasing aboral transit as pregnancy proceeded. Bueno and Ruckebusch,[4] using chronically implanted electrodes in the small intestine of fetal sheep and dogs to measure myoelectric activity (*in utero* and after birth) showed quite clearly that motor activity developed according to a species specific gestationally dependent pattern. The first direct studies in the human using single lumen nasojejunal (NJ) silastic feeding tubes in infants born prematurely,[5] showed that a similar gestationally dependent progression was present in the human neonate.

Using a multilumen manometric technique we have assessed more fully the development of fasting small intestinal motor activity in a group of preterm infants.

Methods

SUBJECTS

Twelve preterm infants (aged 28–42 weeks gestation, weight 800–3260 g) were studied, nine longitudinally (three subjects on four occasions, one on three occasions, five on two occasions) and three on a single occasion, with a total of 28 separate observations. All but the most severely ill infants were included in the study and no infant was studied on more than four occasions. The study was approved by the Standing Ethical Committee, St Mary's Hospital. Informed consent was obtained from the parents for each infant before study.

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The infants were all fasted before study. In most infants this was between four to 24 hours but in a few of the smaller totally enterally fed infants, a fast of two hours only was possible if hypoglycaemia was to be prevented. Very soft polyvinyl chloride (PVC) multilumen catheters [od 1·5 mm, id 0·7 mm (double channel) 0·5 mm (triple channel) Dural Plastics, NSW, Australia] were used in 25 studies and single lumen 5 FG silastic feeding tubes were used in three studies. The distal perfusion ports were 2·5 cm apart.

The manometric catheter was perfused with Na Cl 150 mmol/l, at a rate of 0·4 ml/channel/h delivered by a syringe pump system (Harvard Infusion Pump, Boston, Mass., USA). Pressure changes were measured by external Luerlock Mk 3 pressure transducers (Gaeltec, Scotland) and the signal was displayed on a multichannel oscillographic chart recorder (Washington MD4, UK Ltd). The pressure signals were simultaneously digitalised by a 4 channel 10 bit analogue to digital (A-D) converter on a BBC microcomputer (Acorn Computers Ltd, UK) at a frequency of 1 Hz and the data captured on floppy disc for subsequent display and analysis.

The manometric catheters were advanced blindly into the stomach and, while recording pressure changes, further advancement through the pylorus and into the duodenum was monitored by the characteristic change in the frequency of motor activity from three cycles per minute (cpm) in the stomach to 12 cpm in the duodenum. In four of the smaller infants the tube position was further confirmed by radiographic examination when carried out for another primary clinical reason. In each case the tip of the catheter was at the duodenojejunal flexure.

ASSESSMENT OF MOTILITY

The level of development of motor activity was independently assessed in a blind fashion by two of the authors (WMB, PJM) and scored between 1–4. This score reflected the major developmental phases that were seen with 1 representing random activity, 2 clustered phasic activity, 3 prolonged phasic activity, 4 MMC activity. The results obtained by each observer were very similar and never varied by more than 1 scoring unit. These stages are shown in Figure 1.

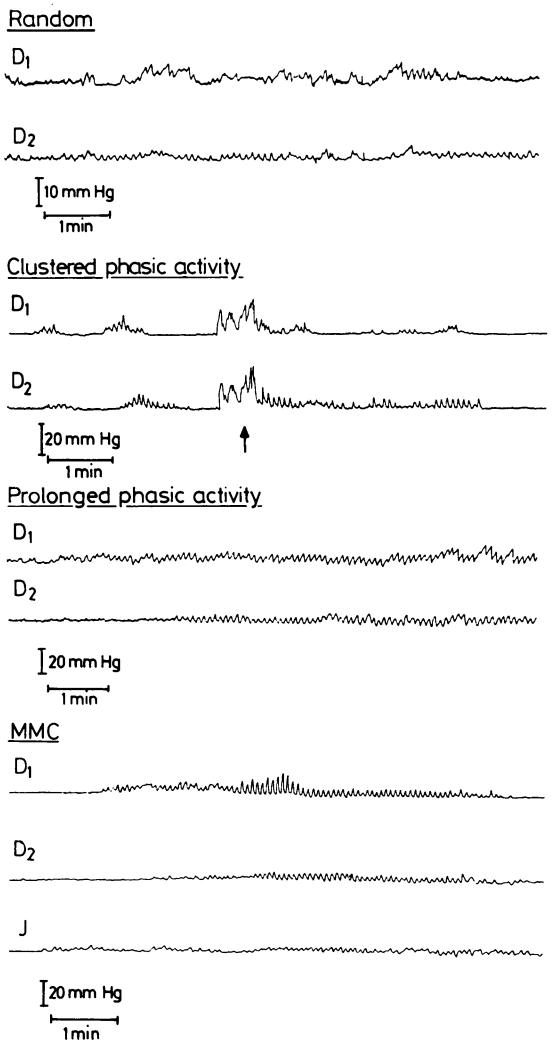

Fig. 1 *Small intestinal pressure recordings showing (1) random (2) clustered phasic activity (3) prolonged phasic activity and (4) MMC activity. (↑) Body arousals frequently occurred during phasic activity. D_1, D_2 are proximal and distal duodenal ports. J is jejunal port.*

Table 1 *Stages of small intestinal motor development with corresponding gestational ages*

Pattern of motor activity	*Number studied*	*Gestational age (wks)*	
1 Random	5	28–32 (29·5)	*
2 Clustered phasic activity	11	28–35 (31)	*
3 Prolonged phasic activity	5	34–36 (35)	*
4 Migrating motor complex	7	37–42 (39)	*

Data are expressed as range (median); *p<0·01 Mann-Whitney U Test.

The degree of propagation of motor activity was assessed visually with a score of 0 reflecting no propagative activity and a score of 5 reflecting well organised propagative activity. The frequency of fasting duodenal motor activity was measured both by visual planimetry and computerised methods. The digitalised pressure data underwent 512 point fast Fourier transformation and the major peak of the power spectrum was derived. The visual and

computerised frequency determinations were very similar.

The clinical condition of the patients studied varied from those infants on ventilators or other respiratory support who were designated as 'ill' to healthy normal preterm infants who were designated as 'well'.

The gestational age denotes the corrected postconceptual age.

STATISTICAL ANALYSIS

Linear regressional analysis was used to calculate the correlation between gestational age and intestinal pressure and frequency parameters with the significance of these relationships being tested by the F test. The relationship between the motor development score and motility parameters was derived by non-parametric analysis of the median values for each motor group. The level of propagated activity was similarly analysed. The difference between non-parametric variables was tested with the Mann-Whitney U test. Data are expressed as the range and median value.

Results

Despite the narrow lumen of the catheters used, there was no attenuation of the manometric recordings. Artefacts were present due to body movements such as arousals, and startles, and to crying. Despite such artefacts, differing patterns of motor activity at differing gestational age were clear and 4 stages of development could easily be discerned (Table 1), although there was considerable interindividual patient variation of motor activity there were very little inter observer differences in assessment of the records.

Before 31 weeks gestational age low amplitude random contractions without obvious organisation and little evidence of propagation were recorded. Between 31–34 weeks gestation and very occasionally as early as 28 weeks some organisation of muscle contraction began to appear with the development of clustered phasic contractions. This is similar to the 'fetal pattern' described by Bueno in the experimental animal.[4] Such activity lasted between 1–20 (median four) minutes and occurred every 4–35 (median 12) minutes with a frequency of motor activity of 10·5–11·5 (median 11) cpm. Initially about 50% of clustered contractions were propagated aborally but by 34 weeks this number was greatly increased and at least 90% were propagated aborally.

With increasing postconceptual age the clusters of phasic activity became longer, the frequency of contractions increased (11·5–12·5 median 11·7 cpm) and prolonged phasic contractions were seen variably between 34–36 weeks gestation. The nature of this prolonged phasic activity and the cyclical character of the fasting motor activity observed at about 35 weeks postconception was, however, poorly developed with intervals between activities varying between 4–30 (median 12) minutes and the duration varying from only five minutes to very long periods of phasic activity lasting up to 40 minutes (median 12 minutes). All phasic activity recorded was, however, aborally propagated.

By term well defined fasting motor activity was present with clearly discernable phase I, II, and III present. The length of phase III activity was now much less variable, three to seven (median four) minutes, and the interval between phase III was 18–45 (median 25) minutes. The data regarding motor complex length, interval, contractile frequency, and propagation velocity are summarised in Table 2.

The development of motor activity seen in the 28 motility studies when plotted against the gestational age of the infants is shown in Figure 2. Straight lines join the results obtained in the same patient when studied on more than one occasion. In all the patients

Table 2 *Complex length, interval, motor frequency and propagation velocity for each stage of motor development. Motor organisation (1) random (2) clustered phasic activity (3) prolonged phasic activity (4) MMC*

Motor organisation	*Complex length (min)*	*Complex interval (min)*	*Motor frequency (cpm)*	*Propagation velocity (cm/min)*
1	0	0	10·5–11·5 (11·0)	0
2	1–20 (4)	4–35 (12)	10·5–12·0 (11·0)	0–5 (2·5)
3	5–40 (12)	4–30 (12)	11·5–12·5 (11·7)	1–5 (1·4)
4	3–7 (4)	18–45 (25)	11·0–12·5 (12·0)	0·7–7·5 (2·5)

Values expressed as range (median); *p<0·05 Mann-Whitney U Test.

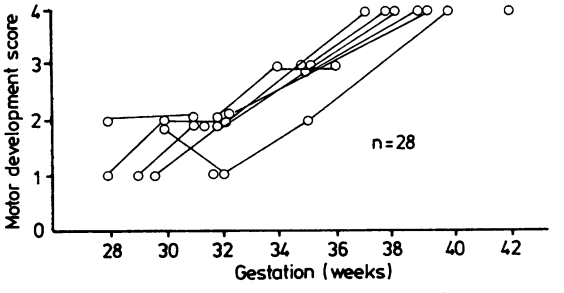

Fig. 2 *Changes in motor development score with increasing gestational age. (1) random (2) clustered phasic activity (3) prolonged phasic activity and (4) MMC activity. Longitudinal studies joined by straight lines.*

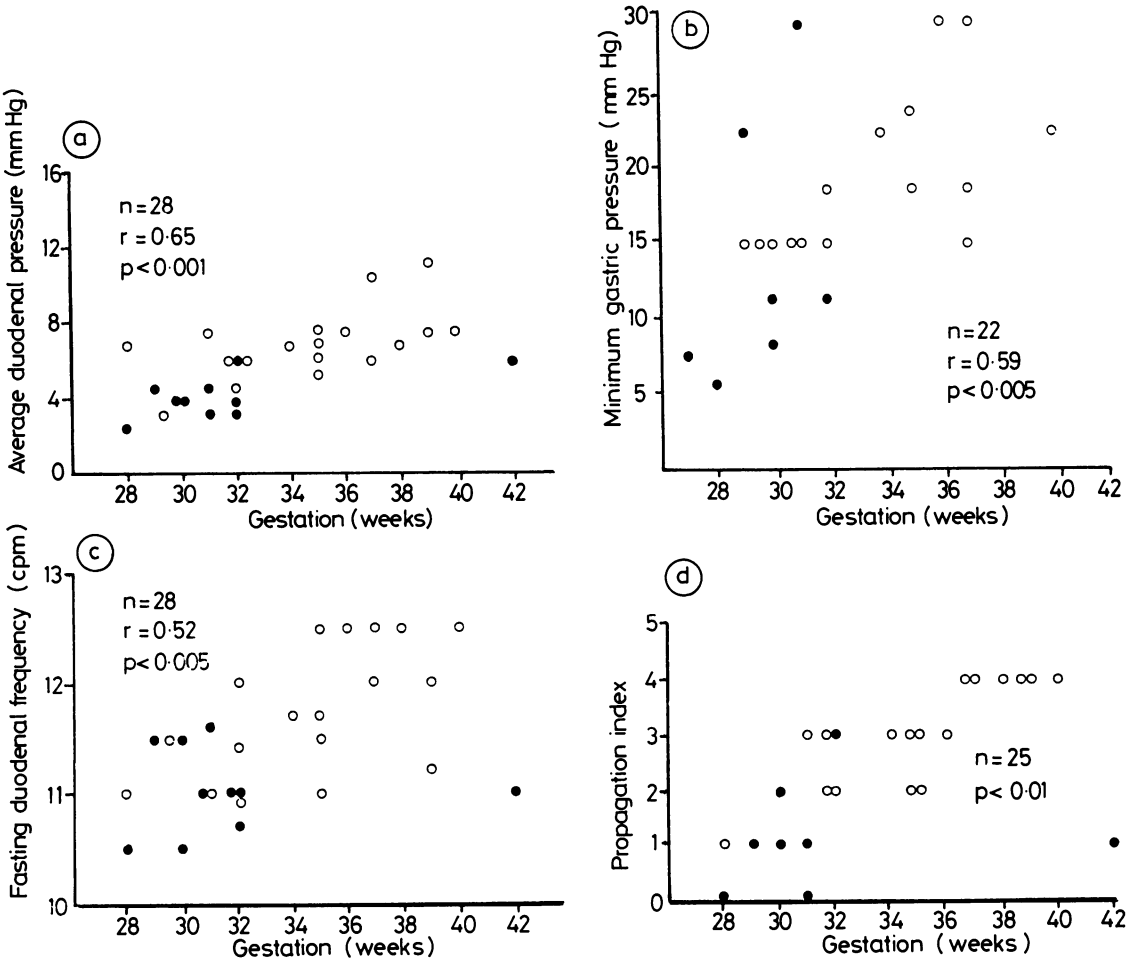

Fig. 3 *Changes in (a) duodenal pressure, (b) gastric antral pressure, (c) fasting duodenal frequency, and (d) propagative activity with increasing gestational age. (p<0·01) 0 'well' infants ● 'ill' infants.*

who were studied on more than one occasion there was an obvious rise in the development motor score with increasing postconceptual age. Non-parametric analysis of infants from each developmental group shows a significant rise in median gestational age with the more mature motor patterns (see Table 1). Normal small intestinal motor function relies on the integration of smooth muscle, enteric nervous system and the humoral environment of the gut. Indirect measurement of the development of each of these individual components of the motor apparatus with increasing gestation is shown in Figure 3a, b, c, d where a significant ($p<0·01$) relationship can be seen.

Smooth muscle development was assessed by measuring contractility as judged by the average pressures generated within the duodenum and the maximal pressures generated within the antrum of the stomach. These results are plotted in Figure 3a and 3b and show a clear rise in upper gastrointestinal contractility with increasing gestational age. The slow wave frequency or basic electric rhythm (BER) increased with increasing gestational age from 10·5 cpm to 12·5 cpm (Fig. 3c). In Figure 3d a clear rise in the level of propagative index can be seen.

It is interesting to note that the one outlier in Figure 3 who had reduced duodenal pressure, contractility and frequency was an ill 42 week infant on a ventilator. Clinically ill preterm infants have reduced enteral feed tolerance but with the relatively small number of patients studied it was not possible to elicit statistically significant differences in small intestinal motility between the 'ill' and the 'well' infants.

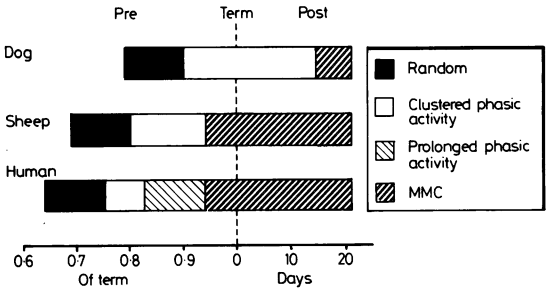

Fig. 4 *Relative maturation of motility patterns in man, sheep, and dog.*

Discussion

The ontogeny of fasting small intestinal motor activity in man shows evidence of a species specific programme of development with a clear pattern of maturation with increasing gestational age. The pattern is characterised by an increase in the contractility and frequency of contraction of intestinal smooth muscle associated with an increase in the degree of propagative activity and in the fasting state the eventual development of a cyclical pattern which characterises fasting intestinal motility in older children and adults.[6] The changes in the pattern of motor activity represent the integrated maturation of smooth muscle, the enteric nervous system and their humoral environment.

The results of this study extend those of Milla and Fenton[5] in which only a single lumen silastic enteral feeding tube was used and parallel those found in the fetal dog and sheep by Bueno and Ruckebusch.[4] Initially there was a disorganised phase, followed by regular spiking activity and eventually a migrating motor complex pattern occurred at term in the sheep and 15 days postpartum in the dog. It should be noted, however, that there are many differences in the motor activity of the adult sheep and dog compared with man. In the fasting dog regular phase III activity occurs with much greater regularity than in fasting man and in the sheep phase III activity occurs in the fasted and fed state. In spite of these differences, however, the patterns of activity recorded in fetal sheep and dogs provide a valuable model for the study of the ontogeny of small intestinal motor activity in the human infant. The disorganised patterns of low grade activity which were seen in infants of under 30 weeks gestation are similar to the disorganised spiking activity that occured in sheep from 0·6–0·8 of term and from 0·8–0·9 of term in dogs. This same gestational age is generally associated with poor tolerance of enteral nutrition in man and is associated with marked delay in intestinal transit as previously shown by amniography.[3] The repetitive bursts of activity seen between 31 and 34 weeks gestation may be analogous to migrating action potential complexes (MAPC) described in older human subjects.[7] The phase intermediate between the period of clustered phasic activity and the development of the migrating motor complex (MMC) pattern was one of great variability in complex and cycle length and may reflect an immaturity of enteric nervous and humoral control systems. It is only towards term that this variability begins to disappear (Table 2).

The initiation of the clusters of phasic activity which then became longer and longer may be humorally mediated and it has been shown that secretion of a number of polypeptide hormones which may be involved with intestinal motor activity occurs at about this gestational age.[8] Propagation and the subsequent shortening of the duration of prolonged phasic contractions with emergence of MMC activity is, however, much more likely to be caused by the development of inhibitory networks in the enteric nervous system. In the sheep and dog there is evidence that with increasing gestation there is a three-fold increase in cycle length of the fasting programme of proximal small intestinal motor activity.[4] Such a change in the cyclical activity of the enteric nervous system of the proximal small intestine has been associated with the development of serotoninergic networks in the calf and sheep.[9,10] There is no information regarding the development of such networks of the enteric nervous system in man but an increase in the fasting cycle length from 12 minutes at 31 weeks to 25 minutes at 39 weeks is also seen in man. It is entirely possible that this is similarly associated with the development of serotoninergic neurones in the proximal small intestine.

The relative development of fasting small intestinal motility in man, sheep, and dog is shown in Figure 4. It is clear that there is a predetermined timetable of development in each species. In the human infant the close relationship between gestational age and motor development seen in our study supports the presence of such an inherent programme and confirms previous animal studies[10] that birth has little effect on fasting intestinal motor activity.

The stage of intestinal motor development can be predicted from the gestational age of the child in much the same way as neurological development can be determined from the Dubovitz score.[11] Until recently our knowledge of the ontogeny of intestinal motor function has been very scanty and thus feeding regimes in preterm infants have been based more on local dogma than a firm understanding of the physiological processes involved. As the level of motor activity correlates extremely well with the ability of

the gut to tolerate feeds the data presented here should be of value in planning the introduction of enteral feeds to preterm infants.

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