# FEEDING PRACTICES, NUTRITION AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AMONG NEWBORN INFANTS IN NEONATAL UNITS

By

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**ABSTRACT**

With improved care, infants born preterm are likely to survive both in high and low-resource settings. However, rate of postnatal growth failure is known to be high around the world although studies in Southeast Asia are still lacking. Effective interventions are needed to ensure that preterm infants can grow optimally. Nutrition, as one of the most important aspects in the postnatal care of preterm infants should be the top priority. Application of feeding practices varies, due to the differing protocols in neonatal units and medical conditions of the infants. In my first study (Chapter 2), nutritional practices and intakes among preterm infants in the neonatal units in Malaysia and the UK are compared and the association with growth at discharge was analysed. Results have shown that a higher number of Malaysian infants received breast milk (Malaysia: 98%, UK: 76%, p=0.001) and parenteral nutrition (Malaysia: 80%, UK: 38%, p<0.001) during admission**.** Malaysian infants received more protein (3.0 vs 2.7g, p=0.004) and had fewer energy and protein deficits (-191.6 kcal/kg vs -254.5 kcal/kg, -11.4 g/kg vs -15.4 g/kg) on week 1-4 of life as compared to infants in the UK unit. Despite this, more than half of infants in both units were discharged with growth failure, defined as a change in weight-for-age Z-score (WAZ) of >-1.28. Infants who had a longer length of stay had a larger drop in WAZ in the Malaysia unit. This relationship was not found in the UK cohort where protein intake and protein energy ratio (PER) were the variable that associated with changes in WAZ between birth and discharge.

From the first study, the differences in breast milk use between the neonatal units were highly apparent. Therefore, I designed the next study to look at breastfeeding in the UK neonatal unit in more detail (Chapter 3). Here, a retrospective observational study in a neonatal unit in the UK using the BadgerNet database was

conducted on the prevalence of breastfeeding between 2017 and 2020. This included the duration when the COVID-19 pandemic had started, allowing me to investigate any changes of practices associated with it and the impacts on the prevalence of breastfeeding in the neonatal unit. Results have shown that there were fluctuations in the breast milk feeding prevalence during admission (adjusted OR of 0.70 (95% CI 0.44-1.12, p=0.140) and at discharge (adjusted OR of 0.96 (95% CI 0.62-1.47, p=0.844) during the early COVID-19 pandemic period as compared to the pre-pandemic period, but this was not significant. This could be due to the small sample size in this study which may not be sufficiently powered to detect a difference between the periods, or other factors such as the breastfeeding policies in the study unit which follows the WHO recommendations.

The next study also involved the use of a database as a part of the study of feeding practices in neonatal units. Gastro-oesophageal reflux (GOR) is a common condition that affects feeding practices in preterm infants and may impact their growth. It is called gastro-oesophageal reflux disease (GORD) if it presents with complications. In this study (Chapter 4), I used the National Neonatal Research Database (NNRD) to describe patterns of GORD diagnosis and use of anti-reflux medications among preterm infants in England and Wales from 2010 to 2017. Results have shown that more infants receive anti-reflux medication (10-14% of infants) as compared to those who had a GORD diagnosis (4-5% of infants). There was a decreasing trend in the use of anti-reflux medications since 2010, with the most rapid decline occurring after 2013. From this chapter, the patterns of use of different types of anti-reflux medications including Histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPI) were also demonstrated.

In parallel to this work, I wanted to find out about the current practices and perspectives of management of GORD in preterm infants in the UK. For this, I

conducted a two-part scoping survey which was undertaken as a patient and public involvement activity comprised of: i) health practitioners' perspectives on the management of GORD and anti-reflux medications use in neonatal units, and ii) parents' perspectives on the treatment of GORD received by preterm infants during admission in neonatal units (Chapter 5). This study demonstrated the diversity in opinions among health practitioners in determining the signs and symptoms related to GORD. However, self-reported strategies used in their clinical practice were quite consistent. The majority of respondents reported that they do not use anti-reflux medications and preferred a trial of a non-pharmacological approach before pharmacological management (n=80/154 (52%)). A few of the respondents noted that GORD is a self-resolving condition, and they would never treat it. In terms of pharmacological therapy, PPI and feed thickener with antacid (i.e. Gaviscon) were the two most popular (PPI: n=100/154 (65%), Gaviscon: n=93/154, (60%)) and prokinetics (n=27/154 (18%)) were the least medication used. The parents' survey generally showed that parents have a certain level of understanding of the importance of using non-pharmacological strategies on initiating the treatment for GORD. However, further information and reassurance are needed to explain to parents why using medications should not be viewed as the most direct method in managing GORD in these infants.

In conclusion, my work has demonstrated findings in two main area of neonatal research which affects all neonates (i.e. importance of feeding and growth) and a clinical problem (i.e. GORD) which affects large number of infants. Infants' characteristics and feeding practices were shown to be varied between the neonatal units studied in the UK and Malaysia and these could impact nutritional requirements and growth outcomes of preterm infants. Current nutritional practices often do not meet recommended intakes and affecting their growth at discharge, especially for protein in preterm infants. However, considering the small sample size

and the exploratory nature of this study, the findings should be interpreted with cautions, while also taking into consideration that feeding plan, growth and discharge decision in the units is not a linear pathway and there are other external factors that might affect one pathway or another. In terms of the prevalence of breastfeeding in the neonatal unit in the UK, this study has shown that the effect of COVID-19 pandemic on the rate of breastfeeding was not apparent and the fluctuations were not statistically significant. Larger sample size with the inclusion of more study units might provide a better analysis of the variations observed. Lastly, in the study of GORD and the use of anti-reflux medications among preterm infants, I have shown a discordance between GORD diagnosis and the use of anti-reflux medications. This could be a reflection of difficulties in diagnosing the condition and the lack of evidence-based management strategies. The parents and health care professionals survey supported this. Further research should be guided to design clinical diagnostic tools and evidence-based strategies to manage GORD in preterm infants.

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**DECLARATION**

The work in this thesis was completed within the Lifespan and Population Health, School of Medicine, University of Nottingham (Queen Medical Centre) and Neonatal Unit, University Hospitals of Derby and Burton (Royal Derby Hospital) between May 2019 and June 2021.

Unless otherwise specified, this thesis demonstrates my work that was achieved under the supervision of Dr Shalini Ojha, Professor Helen Budge and Dr Lisa Szatkowski.

To the best of my knowledge, this thesis is an accurate representation of the work performed, and no other study reproducing this work has been carried out within the University of Nottingham.

Haslina Binti Abdul Hamid

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## PRESENTATIONS AND PUBLICATIONS

### Oral presentations

**Abdul Hamid, H.**, Budge, H. and Ojha, S. Feeding the Preterm Infants: What is the Optimal Growth? Medicine and Health Sciences Faculty Postgraduate Research Forum, School of Medicine, University of Nottingham. May 2019.

**Abdul Hamid, H.,** Budge, H., Szatkowski L., Cheah FC., and Ojha, S. Feeding the Preterm Infant: Can we achieve adequate growth by hospital discharge? Sue Watson Postgraduate Presentation Prize, School of Medicine, University of Nottingham. June 2021.

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### Poster presentations

**Abdul Hamid, H.,** Abramson J., Smith, C., Budge, H. and Ojha, S. Nutrition in the First 4 Weeks of Life for Preterm Infants: Effects on the Growth at Discharge. Division of Child Health, Obstetrics and Gynaecology, Research and Impact Highlights Programme, School of Medicine, University of Nottingham. February 2020.

**Publications**

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**Abdul Hamid, H**., Szatkowski L., Budge, H. and Ojha, S**.** Impact of the COVID-19 pandemic on breastfeeding during and at discharge from neonatal care. (under review)

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| | |
|---|---|
| AA | Amino acid |
| AAP | American Academy of Pediatrics |
| ACOG | American College of Obstetrics and Gynaecology |
| AGA | Appropriate for Gestational Age |
| ALA | A-linolenic acid |
| AOR | Adjusted odds ratio |
| BAPM | British Association of Perinatal Medicine |
| BFHI | Baby Friendly Hospital Initiative |
| BM | Breast milk |
| BMF | Breast milk fortifier |
| BNF | British National Formulary |
| BPD | Bronchopulmonary dysplasia |
| C-hets | Caring Hospital Enterprise System |
| CA | Corrected age |
| CGA | Corrected gestational age |
| CI | Confidence interval |
| CLD | Chronic lung disease |
| COVID-19 | Coronavirus disease caused by SARS-CoV-2 |
| CRF | Clinical Record Forms |
| DBM | Donor's breast milk |
| DHA | Docosahexaenoic acid |
| DOL | Day of Life |
| EBM | Expressed Breast Milk |
| EFAs | Essential fatty acids |
| EHPF | Extensively hydrolysed protein formulas |
| ELBW | Extremely low birth weight |
| EN | Enteral Nutrition |
| EPR | Electronic patient record |
| ESPGHAN | European Society for Paediatric Gastroenterology Hepatology and Nutrition |
| EUGR | Extrauterine Growth Restriction |
| FDA | Food and Drug Administration |
| FM | Fat mass |
| GA | Gestational age |

| | |
|---|---|
| GOR | Gastro-oesophageal reflux |
| GORD | Gastro-oesophageal reflux disease |
| GPRD | General Practice Research Database |
| H2RA | Histamine-2 receptor antagonists |
| HC | Head circumference |
| HCTM | Hospital Canselor Tuanku Mukhriz |
| HDC | High Dependency Care |
| HIE | Hypoxic-ischemic encephalopathy |
| ICD-9 | International Classification of Diseases, Ninth Revision |
| Ig | Immunoglobulins |
| ILE | Intravenous lipid emulsions |
| IUGR | Intrauterine Growth Restriction |
| IQR | Inter-quartile range |
| IVH | Intraventricular haemorrhage |
| LA | Linoleic acid |
| LAZ | Length-for-age Z-scores |
| LBW | Low Birth Weight |
| LC-PUFA | Long chain polyunsaturated fatty acids |
| LES | Lower oesophageal sphincter |
| LGA | Large for Gestational Age |
| LOS | Late onset sepsis |
| LSRO | Life Sciences Research Office |
| MCT | Medium- chain triglycerides |
| MD | Mean or Median difference |
| MHRA | Medicine and Healthcare products Regulatory Authority |
| MNNR | Malaysian National Neonatal Registry |
| MOM | Mother's own milk |
| NASPGHAN-ESPGHAN | North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition NASPGHAN and ESPGHAN combined |
| NDAU | Neonatal Data Analysis Unit |
| NEC | Necrotising enterocolitis |
| NHMS | The National Health and Morbidity Survey |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |

| | |
|---|---|
| NICU | Neonatal Intensive Care Unit |
| NNAP | National Neonatal Audit Programme |
| NNRD | National Neonatal Research Database |
| OR | Odds ratio |
| PDA | Patent ductus arteriosus |
| PER | Protein energy ratio |
| PGF | Postnatal Growth Failure |
| PHIS | Pediatric Health Information System |
| PIC | Paediatric Intensive Care |
| PMA | Postmenstrual age |
| PN | Parenteral nutrition |
| PPE | Personal protective equipment |
| PPI | Proton Pump Inhibitors |
| PVL | Periventricular leukomalacia |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RCPCH | Royal College of Paediatrics and Child Health |
| RDH | Royal Derby Hospital |
| ROP | Retinopathy of prematurity |
| RR | Risk ratio |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus-2 |
| SCCI | Standardisation Committee for Care Information |
| SD | Standard deviation |
| SE | Standard error |
| SEA | South East Asian |
| SGA | Small for Gestational Age |
| StRONNG | Standardised Reporting of Neonatal Nutrition and Growth outcomes |
| TEE | Total energy expenditure |
| THIN | The Health Improvement Network |
| THIS | Total Hospital Information System |
| TLESR | Transient lower oesophageal sphincter relaxation |
| TPN | Total Parenteral Nutrition |
| US CDC | US Centers for Disease Control |
| VIF | Variance inflation factor |
| VLBW | Very Low Birth Weight |
| WAZ | Weight-for-age Z-scores |
| WHO | World Health Organization |

# CHAPTER 1: INTRODUCTION

## 1.1 Definition and Classification of Preterm Birth/Infants

According to the World Health Organization (WHO), preterm birth can be defined as 'all births before 37 completed weeks of gestation, or fewer than 259 days from the first date of a woman's last menstrual period' (1). Gestational age (GA) is the time elapsed between the first day of the last normal menstrual period and the day of delivery and expressed in completed days or completed weeks (2).

Based on this GA definition, preterm infants can be categorised into three or four groups (3,4) which are:

- extremely preterm (<28 weeks)
- very preterm (28 - 31 weeks)
- moderate preterm (32 - 33 weeks)
- late preterm birth (34 - 36 completed weeks of gestation)

Additionally, preterm infants can also be classified based on birth weight (4), which are:

- extremely low birth weight (ELBW) (< 1000 g)
- very low birth weight (VLBW) (< 1500 g)
- low birth weight (LBW) (< 2500 g)

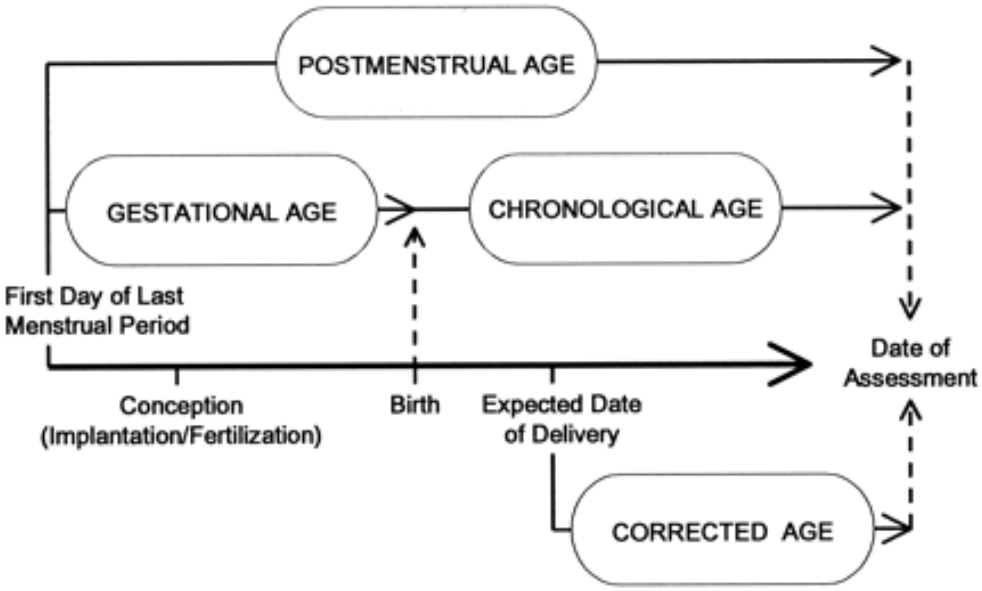
However, using birth weight alone, instead of GA, to determine the degree of prematurity might be inappropriate as there are several conditions that may result in LBW in preterm infants, which include : (i) growth deceleration in utero, causing intrauterine growth restriction (IUGR), (ii) steady growth in utero but below the

normal range, which could cause small for gestational age infants (SGA), or (iii) preterm birth with a weight appropriate for gestational age (AGA) (5).

In light of the possible overlaps in the causes of infants being of LBW, and being born at preterm gestations, an earlier international definition of prematurity suggested (birth weight ≤2500 g) was changed by WHO so that infants born early and those born small for their GA can be distinguished (6).

In the literature where descriptions of the length of gestation and age in infants are explained, a few terminologies can be found and these are defined as below (2) and showed in Figure 1.1:

i. gestational age (GA) (or menstrual age) - the time elapsed between the first day of the last normal menstrual period and the day of delivery
ii. chronological age (or postnatal age) - the time elapsed after birth
iii. postmenstrual age (PMA) - the time elapsed between the first day of the last menstrual period and birth (gestational age) plus the time elapsed after birth (chronological age)
iv. corrected age (CA) (or adjusted age) - represents the age of the child from the expected date of delivery, calculated by subtracting the number of weeks born before 40 weeks of gestation from the chronological age
v. conceptional age - the time elapsed between the day of conception and the day of delivery.




Five different terminologies in explaining the length of gestation and age in infants. Figure from (2).

**Figure 1.1: Terminologies on length of gestation in infants**

## 1.2 Prevalence and Causes of Preterm Birth

Every year, it is estimated that 15 million infants are born preterm (4). In addition, approximately 1 million deaths of children involving the complications of preterm birth were recorded globally in 2015 (7). This puts preterm birth complications as the leading cause of perinatal mortality and morbidity and death among children under 5 years of age, encompassing approximately 16% of all deaths under 5 years of age and 35% of deaths among infants (≤1-year-old) in 2016 (7).

Global estimates initiated by WHO for preterm birth shows that c.11% of live births around the world were preterm in 2014 with more than 80% of preterm births occurring in Asia and sub-Saharan Africa (8). By gestational age group, over 84% of preterm births occur at 32–36 weeks of gestation, less than 5% at < 28 weeks' gestation and the other 10% at 28–32 weeks of gestation (9). India, China, Nigeria,

Pakistan, Indonesia, and the United States contribute to 50% (c.7.4 million) of the total preterm births in the world (11). However, these rates need to be interpreted with caution as there is indeed a strong justification to improve the quality and volume of data for preterm birth rates. There are variations found in many countries in terms of standardisation of definitions, measurement, and reporting of preterm birth rates. Additionally, as in the WHO report as above, the use of civil registration and vital statistics (CRVS) data as preferred data source serve as a limitation as not all countries have this system which leads to the inclusion of non-population-representative data (such as research studies) which is not ideal and might affect the true estimates (8).

There are two main causes that lead to preterm birth that have been suggested. The first is spontaneous, which is due to the natural onset of labour or caused by prelabour premature rupture of membranes (PPROM). The second one is provider-initiated preterm birth, which is preterm labour induced before 37 completed weeks of gestation (urgent or discretionary) due to maternal or fetal compromise or other non-medical reasons (10). Spontaneous preterm births constitute 70% of preterm births in high-income countries and include those following spontaneous labour, spontaneous rupture of membranes and spontaneous dilation of the cervix outside the context of labour (11).

Some proposed risk factors that are associated with preterm birth include multiple gestations, short inter-pregnancy gaps, extremes of maternal age (young or old), technology-assisted pregnancy, history of preterm birth in a prior pregnancy or a family history of preterm birth, substance and tobacco use in pregnancy, low socio-economic status, and clinical factors such as periodontal disease, bacterial vaginosis, or malnutrition and poor pregnancy weight gain (11).

Impacts of preterm birth lie in its short- and long-term complications and how severely prematurity affects the infant's survival, growth and development. The development of organ systems is directly related to gestational age and the complications associated with preterm birth reflect the immaturity of the main organs such as the brain, lungs, gastrointestinal system, immune system, kidneys, skin, and eyes (12). There is a higher risk of getting most complications with decreasing gestational age and lower birth weight (14).

However, ensuring survival is only part of optimal neonatal care. Now that a large proportion of infants born preterm, including those of lower GA who are likely to survive with the availability of neonatal intensive care (13), further effective interventions are needed to ensure that they can grow healthily. Nutrition, as one of the most important aspects in the postnatal care of preterm infants, should be a high priority amongst other efforts to reduce morbidities (4).

### 1.3 Common Nutritional Practices in Neonatal Units

The goal of nutritional care for the preterm infant is to provide necessary nutrients to match the growth trajectories (weight, head circumference (HC), length), body composition as well as developmental outcomes of the normal healthy fetus of the same gestational age (14). This is usually achieved by the use of intravenous (IV) feeding or commonly known as parenteral nutrition (PN) for some preterm infants, as well as the enteral feeding or enteral nutrition (EN) of breast milk or formula milk.

In preterm birth, the fetus is abruptly transitioned to a preterm infant, which leads to an interruption of nutrient supply when the cord is clamped. In order to avoid any detrimental malnutrition during this period, a growing body of literature supports the minimisation of nutrition interruption by providing appropriate nutrition in the form of

PN or EN as soon as possible after birth (15). It is also recommended that nutrients should be delivered at the same rate as the infant would receive in the womb to maintain the anabolic state and to avoid the “metabolic shock’’ that could result from the sudden interruption of continuous supply of nutrition (15).

Starting EN may help to promote the capacity for feeding tolerance, gastrointestinal mucosal growth and development, as well as improved gastrointestinal motility (16). EN also comparatively carries fewer complications than PN - as the latter is associated with intravenous catheter-related complications such as infections, and sepsis (17). Furthermore, The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee and WHO recommend the use of breast milk for preterm infants and infants as standard practice (18), which can be delivered orally or through EN. However, for extremely preterm infants, EN might not be able to provide adequate nutrients to meet requirements whilst avoiding complications. The introduction of EN in preterm infants is usually affected by concerns about feeding intolerance, gastro-oesophageal reflux (GOR), and/or necrotising enterocolitis (NEC) (19).

NEC is a serious intestinal inflammatory disease in infants that is characterised by inflammation and injury of the gut wall barrier which may lead to necrosis and perforation of the gut (20). While prematurity is a major risk factor for NEC, infants who are clinically unstable or suffering from severe comorbidities may be at a greater risk for NEC. However, NEC usually only occurs after infants have been started on EN (21). This causes concerns and fear of initiating early feeding in at-risk infants especially those who are extremely preterm or most unwell.

Therefore, PN is usually started to initiate delivery of nutrients in extremely preterm infants and VLBW infants who may take a longer time to establish enteral feeds (22). It is also indicated for infants who have been identified or suspected of having gastrointestinal malfunctions such as NEC (22). In general, there are no definite indications in terms of which gestational age or conditions are most suitable for PN, but studies showed that PN is routinely used for preterm infants <30 weeks and/or <1250 birth weight (22).

Some neonatal units might also recommend PN use in infants <32 weeks or <1500g based on their medical conditions, and some would also use it in more mature infants as a 'bridge' towards establishing enteral feeding (22). In the latest UK National Institute for Health and Care Excellence (NICE) 2020 guidelines (23), PN is indicated for infants who were born <31 weeks GA. For infants who were born at, or after, 31 weeks, PN is recommended for infants when insufficient progress is made with establishing enteral nutrition within 72 hours after birth.

The average duration of PN use until full enteral feeding is achieved in typically 1–2 weeks (22), and this duration is closely linked to the degree of prematurity as well as the growth progress (24,25). There have also been many studies that demonstrated improved growth outcomes of preterm infants through adequate protein and energy intakes from PN as compared to PN with fewer nutrients or no PN (26–29). For example, a study by Morgan et al. (26–29) found that early postnatal head growth can be improved with the use of optimised PN regimen (12% glucose, 3.8 g/kg per day protein/lipid) as compared to standard/control regimen (10% glucose, 2.8 g/kg per day protein/lipid) among very preterm infants.

Although PN is essential for providing nutrition to extremely preterm infants and VLBW infants in the early days of life, whenever possible and safe, EN should be

started immediately (22). The transition phase that occurs between the weaning of PN and starting EN (before the full establishment of EN/full enteral feeding) needs to be established with a systematic feeding protocol. This is related to the finding that infants were most susceptible to inadequate nutrition and growth failure at discharge due to suboptimal energy and protein intakes during this phase (30).

### 1.4 Nutritional Requirements and Growth Assessments of Preterm Infants

When considering nutrition requirements for preterm infants to achieve optimal growth, it is important to highlight that many factors may influence their needs. These include age (postmenstrual age (PMA), birth weight status (SGA, AGA or LGA), dietary intakes, accumulated nutrient deficits (both prenatal and postnatal growth restriction), environmental temperature, energy losses, various illnesses, clinical conditions, as well as body composition changes (31). Therefore, providing adequate day-to-day nutrition, and carefully monitoring of growth, are important goals with each infant presenting with their unique conditions and requirements. Failure to provide all the necessary nutrients adequately may lead to not only postnatal growth failure but may also cause an increased in morbidity and suboptimal brain growth with possible neurodevelopment limitations (32,33).

### 1.4.1 Macronutrient requirements

#### 1.4.1.1 Energy

Determination of energy requirements for preterm infants involves careful consideration of the sum of total energy expenditure (TEE) and the energy stored in new tissue for growth (lean and fat mass) and tissue synthesis (43). In order to estimate how much energy and macronutrients infants need, the factorial method has been employed (15). This method uses the fetal body composition model and energy metabolism analysis to derive necessary intakes of protein, energy, major minerals electrolytes. It also sums the requirements for growth with those for the replacement of inevitable losses in urine, faeces, and skin.

From this approach, it has been estimated that the caloric requirements for energy accretion is 24 kcal/kg/d between 24-28 weeks GA, which then increases to approximately 28 kcal/kg/d for the rest of gestation. This leads to a rate of weight gain of approximately 18 g/kg/d between 24-28 weeks. This rate of weight gain then reduces to approximately 15-16 g/kg/d between 32-36 weeks (31) with increasing caloric requirements for lean tissue growth as a result of the fat accretion in adipose tissue that occurs later in gestation. Once protein intake is sufficient to promote net lean body accretion, additional energy from protein will predominantly produce more body fat, which increases almost linearly at energy intakes of more than 80–90 kcal/kg/d in normal, healthy preterm infants (31). It was shown that if energy intakes provided can be maintained at least at 90–100 kcal/kg/d, any deficits in intake below this range is manageable without evident effects in the growth of lean body mass (15).

Therefore, in 2010, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommended a range of enteral energy

intake for healthy preterm infants with adequate protein intake of 110 to 135 kcal/kg/d to match the intrauterine weight gain of 17-20 g/kg/d (35) while the American Academy of Pediatrics (AAP) (2020) (36) recommends around the similar range of 110-130 kcal/kg/d.

However, for preterm infants on PN, a lower energy intake is needed because splanchnic tissue metabolism and stool losses are approximately 30 kcal/kg/d lower than occurs during enteral feeding (37). Therefore, PN energy needs can be met with approximately 90-120 kcal/kg/d, about 10-20% lower than those of enteral needs. When an infant is receiving both PN and EN, it is sensible to disregard the energy provided by EN if the volumes of enteral feed are low (<25 ml/kg/d) (37).

Therefore, based on more recent ESPGHAN PN guidelines (2018) (37), 45-55 kcal/kg/d energy is suggested for preterm infants on day 1 of life and 90-120 kcal/kg/d for the days following. Considering the possibility of energy deficits and the need for catch-up growth especially for smaller preterm infants, most clinicians take 120 kcal/kg/d as their goal to maximise tissue and protein growth (37). Based on AAP (2020) for PN, consensus recommendations, based on weight category are: 105-115 kcal/kg/d for infants <1000g and 90-100 kcal/kg/d for infants 1000-1500g (36).

#### 1.4.1.2 Protein

Early studies showed that preterm infants have very rapid growth rates and protein accretion, which are higher at early gestations before decreasing to the same rate approximately as the term infants (38). Therefore, it was estimated that higher amounts of protein are required for less mature infants and that these will decrease as they grow (16). Based on the factorial approach, it is estimated that the enteral protein intake required for preterm infant growth and protein accretion is at 4 g/kg/d for infants with birth weight less than 1200g and at 3.5 g/kg/d for infants with birth weights of 1200 to 1800g (36,38).

This is consistent with the EN protein intake recommendations of ESPGHAN (2010) (35) which state that high protein intakes are usually needed to compensate for the expected accumulation of protein deficits, especially during the early days of life for less mature preterm infants. Therefore, protein intakes at 4.0 to 4.5 g/kg/d for infants weighing up to 1000g, and 3.5 – 4.0 g/kg/d for infants from 1000 to 1800g are recommended to meet the needs of most preterm infants. In AAP 2020 guidelines (36), the same maximum amount of enteral protein intake up to 4.5 g/kg/d is suggested specifically for VLBW (<1500g) with a minimum of 3.5 g/kg/d.

This is supported by many studies that show that protein intake up to 4.5 g/kg/d among ELBW and VLBW preterm infants can achieve intended extrauterine weight gain (39–42), length gain (43) and this will also help to achieve acceptable plasma albumin and transthyretin concentrations (35). However, a systematic review (38) shows moderate-certainty evidence that protein range of (≥ 4.0 g/kg/d) (very high protein intake) as compared to high protein intake (≥ 3.0 to < 4.0 g/kg/d) in formula

milk-fed infants is related to significantly higher weights and lengths at discharge; while weight gain to discharge was not significantly different (MD 3.10 g/kg/d, 95% CI -0.04 to 6.24). This review was, however, limited as only one study for this comparison was included and three out of 24 infants who received very high protein intake developed uraemia, which was associated with the level of protein intake.

As for PN amino acid intake, ESPGHAN (2018) (44) suggests that amino acid (AA) supply be started on the first postnatal day with at least 1.5 g/kg/d – 2.5g/kg/d to achieve an anabolic state but should be increased between 2.5 g/kg/d to 3.5 g/kg/d from the second day after birth onwards. They also recommend that protein should be accompanied by calories from energy and lipid of more than 65 kcal/kg/d and adequate micronutrient intakes. This is consistent with AAP (2020) recommendations which suggest infusion of 3.5-4.0 g/kg/d of protein for infants <1000g birth weight and 3.2-3.8 g/kg/d for infants with 1000-1500g birth weight.

However, two RCTs have demonstrated that PN infusions higher than 3.5 g/kg/d have not been clearly proved to be of benefit (45,46), though they are not directly proven to be harmful. It is also recommended that, in preterm infants, parenteral AA intakes >3.5 g/kg/d should only be dispensed as part of clinical trials (44).

Therefore, based on the available evidence, a range of approximately 1.5 to 3.5 g/kg/d for parenteral AA alongside intakes from enteral feeding could be an achievable and reasonable clinical strategy to ensure good short-term growth outcomes for preterm infants.

#### 1.4.1.3 Protein Energy Ratio

It is also long known that energy and protein requirements mutually correlate in their importance in synthesising new tissue, for which achieving an adequate protein

energy ratio (PER) is very crucial (35,47). It was demonstrated that if PER is adequate (more than 3 – 3.6 g/100 kcal), an energy intake of more than 100 kcal/kg/d should suffice for preterm infants, although it may achieve fat mass (FM) percentage as in term infants (48). However, as the aim for optimal body composition should be achieving better lean mass growth rather than FM, intakes of more than 140-150 kcal/kg/d should be avoided as they might contribute to excessive deposition of fat mass (48,49).

Based on the ESPGHAN (2010) (35) recommendation for EN energy intake of 110 to 135 kcal/kg/d and protein intake of 3.5 – 4.0 g/kg/d (for infants from 1000-1800g), the matched PER for this range should be 3.2-4.1 g/100kcal/d. However, protein intakes of less than 3.0-3.5 g/kg/d coupled with high energy intakes will still achieve weight gain as in utero but might result in higher fat mass accretion which would be unfavourable for long term health (47,50,51).

#### 1.4.1.4 Lipids

Lipids provide energy, essential fatty acids (EFAs), linoleic acid (LA) and a-linolenic acid (ALA), which are also precursors for longer fatty acids (51). Long-chain polyunsaturated fatty acids (LC-PUFA) such as docosahexaenoic acid (DHA), which accounts for 56% of the lipid mass of neuronal membranes, is important for brain and retina development (51). The delivery of lipid-soluble vitamins - vitamin A, D, E and K also needs an adequate supply of lipids.

For EN, with consideration that recommended upper limits for fat intake should be 54% of energy intakes (which equals to 5.7-6.0g fat/100kcal energy (52,53) as in the maximum range observed in human milk sample), ESPGHAN (2010) recommends that a reasonable range of enteral fat intake for a healthy preterm

infant is between 4.8-6.6 g/kg/d or 4.4-6.0g fat/100kcal energy intakes (40–55% of energy intake), of which MCT is <40% (35).

For PN, intravenous lipids are a vital part of the non-carbohydrate source of energy that should make up 25-50% of non-protein calories in PN (54). Additionally, because of its high energy content per unit volume, intakes in the first week after birth are greatly affected by intakes of IV lipid, where delayed administration of lipid can also lead to calorie deficits and deficiency of EFAs (55). Recent meta-analyses and randomised controlled trials demonstrate evidence that the initiation of lipids within the first two days of life in very preterm infants seems to be safe and well-tolerated, with no increase in morbidities such as sepsis and NEC (29,56).

According to the recent PN recommendation by ESPGHAN (2018) (54), intravenous lipid emulsions (ILE) can be started immediately for preterm infants after birth, no later than on day two of life, should be infused continuously over each 24 hours, but should not exceed 4 g/kg/d.

ILE dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/d is also suggested to prevent EFAs deficiency in preterm infants. In addition, the choice of ILE should be considered in neonatal units based on factors such as the duration of PN, age, morbidities as well as the composition of the respective emulsion itself (54).

#### 1.4.1.5 Carbohydrate

Glucose is a form of carbohydrate which mainly functions as an energy source, especially for the brain and heart. For an infant, the brain utilises almost 90% of glucose of whole-body use. It is also a significant carbon source for the synthesis of

new fatty acids and some non-essential amino acids (35). According to ESPGHAN (2010), 10.5 - 12.0g glucose /100 kcal energy intakes or 11.6–13.2 g/kg/d glucose should come from carbohydrate (glucose or nutritionally equivalent di-, oligo-, and polysaccharides) for enteral feeding (especially measured when using formula milk) (35). Immediate commencement of glucose is required in extremely preterm infants to prevent rapid hypoglycaemia (36).

For PN, it is recommended to start the infusion as soon as possible after birth, at an initial glucose infusion rate (GIR) of 4–6 mg/kg/min and then increased to 8 mg/kg/min subsequently (57). For ELBW infants, 8-10mg/kg/min is suggested as an optimum rate. Higher GIR may cause hyperglycaemia as the process of gluconeogenesis, which starts 24 hours after birth, does not stop even with the supply of exogenous glucose. This occurs even when PN is providing all three macronutrients, including glucose (58). According to the ESPGHAN (2018) recommendation for preterm infants (59), parenteral carbohydrate (glucose) intake should be between 4 mg/kg/min (5.8 g/kg/d) to 12 mg/kg/min (17.3 g/kg/d).

Table 1.1 shows enteral nutrition recommendations by Koletzko et. al. (2014) (60) and other established guidelines from Life Sciences Research Office (LSRO) for the U.S. Food and Drug Administration (FDA) (2002) (53), Tsang et al. 2005 (51), ESPGHAN (2010) (35) and AAP 2020 (36). It appears that there is agreement on recommended rates of most nutrients from these guidelines, except that ESPGHAN‘s recommendations on protein intake are according to the birth weight.

**Table 1.1: Macronutrients recommendations for enteral feeding from 2002-2020**

| Nutrients | Koletzko et al. (2014) (60) | LSRO (2002)(53) | Tsang et al. (2005)(51) | ESPGHAN (2010)(35) | AAP (2020) (36) |
|---|---|---|---|---|---|
| Fluids, ml/kg/d | 135-200 | - | 150-200 | 135-200 | 135-200 |
| Energy, kcal/kg/d | 110-130 | 100-141 | 110-120 | 110-135 | 110-130 |
| Protein, g/kg/d | 3.5-4.5 | 3.0-4.3 | 3.0-3.6 | 4.0-4.5 (<1kg)<br>3.5-4.0 (1-1.8kg) | 3.5-4.5 |
| Lipids, g/kg/d | 4.8-6.6 | 5.3-6.8 | - | 4.8-6.6 | 4.8-6.6 |
| CHO, g/kg/d | 11.6-13.2 | Lactose: 11.5-15.0<br>Oligomers: 4.8-15.0 | Lactose: 3.8-11.8<br>Oligomers: 0-8.4 | 11.6-13.2 | 11.6-13.2 |

ESPGHAN, The European Society for Paediatric Gastroenterology Hepatology and Nutrition (35) ; LSRO, Life Sciences Research Office (53); AAP, American Academy of Pediatrics (36), CHO, Carbohydrate.

### 1.4.2 Types of milk for enteral feeding

#### 1.4.2.1 Breast milk

Breast milk or mother's own milk (MOM) is the best source of nutrition for both term and preterm infants, with numerous health benefits in the short and long term (61,62). ESPGHAN (63), AAP (61) as well as the WHO (4) agree that a mother's own milk should always be the first choice of milk in feeding preterm infants. In addition to its balanced nutritional composition, it contains important substances such as immunoglobulins (Ig)A, lactoferrin, cytokines, enzymes, growth factors and leucocytes (64) that provide protection against infection while also promoting intestinal adaptation and maturation (65). Breast milk also contains numerous "prebiotic" substances such as human milk oligosaccharides (HMO; composed of the five monosaccharides glucose including galactooligosaccharides) that support the growth of non-pathogenic "probiotic" microorganisms, primarily lactobacilli and

bifidobacteria, while removing the potentially pathogenic bacteria (64). This high concentration of HMO is unique to humans in which studies have shown that breastfed infant has a more stable and constant population of oligaosaccharides compared with infants fed with formula milk.

Breast milk feeding also has been linked to improved long-term neurocognitive development (66,67) and cardiovascular health outcomes (63). Additionally, numerous studies have demonstrated the effectiveness of breast milk in offering protection for preterm infants in the NICU against the most common morbidities such as NEC and sepsis (68,69), retinopathy of prematurity (ROP) (70,71) and bronchopulmonary dysplasia (BPD) (72), as well as improved feeding tolerance (73).

Studies showed that NEC is much more common in exclusive formula milk-fed infants than those fed with exclusive human milk; either with MOM or donor's breast milk (DBM) (63,74). Interestingly, the protective effect of breast milk towards both sepsis and NEC is strongly dose-dependent. This is such that the intakes of > 50% of MOM in the two weeks of life (75), intakes of MOM at >50% enteral feeding in the first five days of life (68) or intakes of >50 ml/kg/d MOM taken longer in duration, i.e. four weeks (69) were associated with a reduction in the occurrence of NEC or sepsis. Additionally, one study (76) revealed that for each 100 ml/kg increase in breast milk intake during the first two weeks of life, the risk of NEC or death after two weeks was decreased by a factor of 0.87. These findings are consistent with the early evidence that indicates even a minimal amount of breast milk may increase the physiological maturation of the gastrointestinal tract (75,77,78).

The composition of breast milk is unique - the concentration of both energy and protein in expressed breast milk is highly variable throughout lactation stages,

between mothers, and even from the same mother (79,80). This breast milk content variability affects mothers who give birth prematurely and at term. The protein content in preterm mother's milk is higher than in term mother's milk during the first days of lactation with maximum MD up to 35% (0.7 g/dl) (81,82) but reduces soon afterwards. Three days after birth, the difference in protein between preterm and term milk is within 0.2 g/dL and, eventually by the 5$^{th}$ to 6$^{th}$ week, milk from both have approximately the same protein content. Moreover, the concentrations of certain nutrients, such as the free amino acids valine, threonine and arginine, as well as antibody-secretory IgA, are higher in preterm mother's milk (83).

The comparison in the composition of protein, lipid and carbohydrate in preterm mother's breast milk between lactation week 1 and lactation weeks 2–8 based on systematically selected data (79) is shown in Table 1.2. The data that provided mean value and ranges of the macronutrient content of preterm breast milk per lactation week in this table were collected only from studies that used 24-h milk sampling (79). This was implemented intentionally to avoid selecting data from studies with different study designs, in which the milk composition might be influenced by the diurnal, within-feed and inter- and intra-maternal variations.

**Table 1.2: Composition of breast milk between lactation week 1 and week 2-8**

| Week | Protein (g/100ml) | Lipid (g/100ml) | Carbohydrate (lactose g/10ml) | Calculated energy (kcal/100ml) |
|---|---|---|---|---|
| Lactation week 1 | 1.90/1.88 | 2.59/2.63 | 6.55/6.55<br>5.66/5.61 | 57.11 |
| Lactation weeks 2-8 | 1.27/1.24<br>(1.02-1.58) | 3.46/3.54<br>(3.25-3.69) | 7.34/7.28<br>(7.11-7.53)<br><br>6.15/6.04<br>(5.93-6.32) | 65.6/65.7<br>(63.27-67.17) |

[±]Data show means/medians of values reported for Lactation week 1 and means/medians (minimum and maximum) of values reported for weeks 2–8. Table adapted from (79)

**Donor breast milk**

Donor breast milk (DBM) is recommended for preterm infants when MOM is not available especially for VLBW preterm infants (18,84). Several studies have demonstrated effects in protection against NEC (85) and better feeding tolerance (74,86) when compared to formula milk.

A systematic review (74) comparing formula milk to DBM for feeding preterm or LBW infants showed that formula-fed infants had higher in-hospital rates of weight gain (MD 2.51, 95% CI 1.93 to 3.08 g/ kg/d), linear growth (MD 1.21, 95% CI 0.77 to 1.65 mm/week) and head growth (MD 0.85, 95% CI 0.47 to 1.23 mm/week). However, there is an increased risk of NEC (typical risk ratio (RR) 1.87, 95% CI 1.23 to 2.85; risk difference (RD) 0.03, 95% CI 0.01 to 0.05; number needed to treat for an additional harmful outcome (NNTH) 33, 95% CI 20 to 100; 9 studies, 1675 infants) with formula milk. There is no effect on long-term growth and neurodevelopment showed in the trials. The analysis, however, included high numbers of infants on nutrient-enriched preterm formulas or many different formulas while only the five most recent trials used nutrient-fortified DBM for comparison. This restricts the implications for practice from this review as the use of fortifiers in DBM is now a common practice in many neonatal units (87).

Additionally, there are reports of benefits in terms of a reduced incidence of bronchopulmonary dysplasia (BPD) (88), late-onset sepsis (LOS) (89) as well as a decrease of days on mechanical ventilation/oxygen (90) with the use of DBM. However, the storage and processing of DBM such as pasteurisation might affect its biologically active components such as IgA, lysozyme, lactoferrin, lymphocytes, lipase, alkaline phosphatase, cytokines, growth factors and antioxidant capacity (91), although its energy and macronutrients contents might not be affected.

Furthermore, human milk, specifically mature breast milk (which is usually the source of DBM), contains insufficient protein at normal enteral feeding rates (160-180 ml/kg/d) and this has been postulated to affect the growth of preterm infants (92).

**Breast milk Fortifier**

Early studies have shown that human milk, specifically its protein content and other nutrients such as calcium and phosphorus, might only be adequate for the growing needs of the preterm infants of 33–36 weeks' gestation but insufficient for the less mature infants of 28–32 weeks' gestation, and for achieving catch-up growth (93,94).

Since then, many studies have come up with interventions and suggestions on optimising nutrition with breast milk feeding. Although higher volumes of breast milk through enteral feeding may be helpful, these might be associated with feed intolerance, gastro-oesophageal reflux, aspiration pneumonia, NEC, or other complications related to fluid overloads such as PDA and BPD.

Therefore, it is recommended that breast milk is supplemented with so-called "fortifier", which may increase the concentration of nutrients especially adding extra protein, energy, and micronutrients such as calcium and phosphorus, to meet nutrient requirements while aiming to improve weight gain and growth, with tolerable fluid volumes (17). The AAP recommends that breast milk should be appropriately fortified for those with birth weights <1500g to aim for intrauterine growth rates (61) and this has also been supported by ESPGHAN (2010) (35).

Most studies suggest that breast milk fortification can be started safely with multi-nutrient fortifiers when the milk volume reaches 50–80 ml/kg/d (65), but protocols vary between NICUs. The main principle in fortifying breast milk is balancing the osmolality and optimising the concentration of nutrients at the recommended feeding volumes of 135–200 ml/kg/d (65).

Human milk fortification is shown to improve weight gain, linear growth, and head growth during NICU stay, as compared with feeding unfortified milk (96). A recent systematic review of RCTs (97) on multi-nutrient fortification of breast milk for preterm infants showed that fortification increases growth during admission for weight gain (MD 1.76, 95% confidence interval (CI) 1.30 to 2.22g/kg/d, low certainty of evidence ); length gain (MD 0.11, 95% CI 0.08 to 0.15 cm/week, low certainty of evidence ); and head growth (MD 0.06, 95% CI 0.03 to 0.08 cm/week, moderate certainty of evidence ). For the risk of NEC, the meta-analysis did not show an effect (typical RR 1.37, 95% CI 0.72 to 2.63; 13 trials, 1110 infants), although the certainty of the evidence was low due to high risk of bias in most trials included.

However, as nutrient requirements are highly variable together with the different composition of each mother's breast milk (or DBM), several fortifiers were developed which differ by the origin of milk used (bovine, human or donkey), by nutrient composition (multi-nutrient fortifiers or supplements of protein, lipids, carbohydrates), and also by methodologies in manufacture (65).

In infants for whom MOM was not available, Sullivan et al. (98) compared an exclusive human milk-based diet (HM100 and HM40) which consisted of the combination of DBM and a human milk-based fortifier at 100 and 40 ml/kg/d respectively, with the use of formula milk and bovine-based milk fortifiers (BOV). Infants in the BOV group had greater weight gain as compared with the HM100 +

HM40 groups, 16.0 ± 7.8 vs 14.3 ± 3.8 g/kg/d, p = 0.051, but there were statistically significantly fewer cases of the combined outcome of NEC or death in HM groups (HM100 (6%), HM40 (8.5%)), than in the BOV (20%) group.

However, in a more recent study (99), a group of preterm infants with birth weight <1250g fed with MOM and/or DBM (as a supplement) were randomly selected either to receive a human milk-based fortifier (HMBF), or bovine milk-based fortifier (BMBF). This study aimed to determine whether the addition of an HMBF to MOM with supplemental DBM would reduce the percentage of infants included who had a major feeding interruption as compared to the addition of a BMBF (in the absence of formula milk use). There were no statistical differences in feeding interruptions between the groups (17/64 HMBF, 20/61 BMBF; unadjusted risk difference: −6.2% (95% CI: −22.2%, 9.8%), or in days of PN, days to full enteral feeding, postnatal growth or NEC ≥ stage 2 (4.7 vs. 4.9%).

Further studies are also continuing to explore whether adding a fortifier to the DBM might make it more advantageous than formula milk for the short and long term growth outcomes (100,101). The latter is considering the efficacy of DBM in reducing the risk of NEC as compared to formula milk, but the lack of protein and other nutrients that might be depleted due to routine pasteurisation and handling of DBM should also be considered.

Furthermore, there is an important need for studies to investigate the most clinically relevant question for preterm infants in neonatal units, that is if the use of DBM, or fortified DBM, is more beneficial rather than using PN while waiting for MOM. It should be worthwhile to consider the impact of using either feeding method on the growth, considering different proportions of nutrients provided and prevention of co-morbidities such as NEC and sepsis.

#### 1.4.2.2 Formula milk

Formula milk, however, remains an easily available alternative to breast milk especially in settings where donor breast milk is still scarce. Formulas are commonly based on cows' milk and usually provide a protein content of 3.0 g/100 kcal (74). There are a variety of formula milk that differ in terms of energy, protein and mineral content but can be briefly categorised as i) standard term formulas designed for term infants, based on the composition of mature breast milk, containing approximately 67 kcal/100 mL to 70 kcal/100 mL of milk and ii) nutrient-enriched preterm formulas, which are energy-enriched up to (up to approximately 80 kcal/100 mL of milk and may be enriched with variable protein and mineral content (74).

In the early study by Lucas et al. published in 1990, it was suggested that infants fed a higher nutrient density formula milk for a minimum period of 1 month could have lasting beneficial effects on neurodevelopment and regional brain volumes (94). The development of preterm formula also started to increase tremendously and became standard feeding in the NICU in the belief that breast milk could not provide enough proteins for preterm infants. However, in early 2000, with emerging evidence that breast milk reduces the risk of NEC and infections as compared to formula, it has become a standard worldwide to use breast milk, preferably MOM, in the hospital/neonatal units (102).

Based on the recommendation by the US LSRO (2002) (53), preterm formula milk should have a protein content of 2.5 to 3.6 g/100 kcal. This would provide a daily intake of 3.0 to 4.3 g/kg/d at a minimum of 120kcal/kg energy intake, which should be sufficient for growth. In addition, the nutrition composition of the preterm formulas is also designed to meet the needs of the preterm infant including

carbohydrate blends that consist of lactose and glucose polymers, fat blends that also contain medium-chain triglycerides (MCT) and the inclusion of adequate vitamin content. However, as explained earlier, there is an absence of oligosaccharides in formula milk (cow's milk), as compared to its abundance in breast milk although the supplementation of formula milk with HMOs is currently available as an alternative.

There is currently no RCT that has compared formula milk with breast milk (103) as it would be unethical to deprive infants of the benefits of breast milk where it is available. Even though formula milk might be able to provide consistently higher levels of measurable nutrients than breast milk, it is less well tolerated due to the interference with gastric emptying and intestinal peristalsis with its higher density nutrient content. It also might cause a delay in the functional adaptation of the gastrointestinal tract and disturb the patterns of microbial colonisation. These were postulated as factors contributing to the higher risk of NEC with formula feeding (20,104,105).

Furthermore, rapid ‘catch-up growth' (i.e. accelerated weight gain) occurs with formula milk feeding raising concerns that this may alter fat distribution in preterm infants with detrimental impacts on metabolic outcomes such as the long-term risk of insulin resistance and cardiovascular disease (106–108).

However, preterm formula milk is a good option for infants when there is no access to breast milk due to its complete nutrient content. Providing preterm infants with formula milk enriched with adequate energy, protein, minerals, and other nutrients may help to promote nutrient accretion and growth. This is particularly important for infants who are IUGR who might have higher nutrient needs or those who have additional nutritional and metabolic requirements due to illness (35,53).

### 1.4.3 Practice of Breast Milk Feeding in Neonatal Units

As discussed previously, breast milk is well-recognised as the best nutrition for all infants and especially significant for preterm or ill infants admitted to neonatal units (109). Studies demonstrated the benefits of breast milk in terms of nutritional, immunological, developmental, gastrointestinal, and psychological aspects to preterm or ill infants (109,110). However, admission to neonatal units poses a highly challenging situation where barriers to receiving breast milk feeding might be more apparent due to many factors. The prevalence of initiation of breastfeeding and duration of breastfeeding among infants in the neonatal units are also shown to be lower than those born healthy or full-term (111,112).

In a population-based cohort study of preterm infants (22–31 weeks of gestation) discharged home from neonatal units in eight European regions (113), it was found that breastfeeding rates ranged from 70% (18% exclusive breast milk) in Lazio (Italy) to 35% (29% exclusive breast milk) in Trent (UK) and 24% (14% exclusive breast milk) in Ile-de-France (France). Furthermore, a multi-centre study in Italy showed breastfeeding rates of high-risk infants at NICU discharge at 66% (114) while the rates range from 50-60% in the US NICUs at discharge (115,116). Additionally, a study also found that there is a correlation between rates of breastfeeding in the NICU and breastfeeding rates recorded at the national level (113).

These variations in breastfeeding rates between countries and even within NICUs might suggest differences commonly observed in the infant and maternal clinical characteristics as well as sociodemographic distinctions (117).

The first apparent factor lies in the characteristics of infants in neonatal units in which preterm infants, who usually make up the majority of infants admitted to the

neonatal units, are known to have latching difficulties due to their immature sucking behaviour, lethargy and difficulties to coordinate breathing and swallowing, which delays the accomplishment of exclusive breastfeeding (118). This, however, depends on the GA of the infants in which a study among infants who were born between 26-31 weeks GA showed that they initiated breastfeeding from 29 weeks PMA while reaching full breastfeeding at a median PMA of 35 weeks (119).

This is further complicated as infants admitted to the unit might need respiratory support from a medical device and are usually fed via a nasogastric tube, before being gradually introduced to bottle, cup or syringe-feeding when their sucking capability developed (117). For infants with other health complications, the establishment of breastfeeding might be more complicated. Studies showed that infants with morbidities and born at lower GA had a lower likelihood of receiving any breast milk at discharge (113,120) and was regarded as a barrier to breastfeeding from the mothers' perspective (121).

Other than that, infants admitted to neonatal units often have prolonged maternal-infant separation usually caused by complications related to birth (122). This leads to a delay in the important process such as having kangaroo care or skin-to-skin maternal-infant contact which is essential to initiate and promote long-term breastfeeding (123–125). Persistent daily skin-to-skin contact is also associated with the earlier establishment of exclusive breastfeeding, while also supporting infants' neurophysiological development (126).

Mothers of infants who are admitted to neonatal units, especially preterm infants, usually need to start expressing their milk soon after birth and this continues for a while until their infants can initiate direct feeding at the breast (127). However, initiating breastfeeding in terms of expressing breast milk is challenging as their ability to produce milk might be compromised by the preterm birth itself (128) or by

their own maternal and delivery issues including having a caesarean delivery, multiple births, and clinical conditions such as high blood pressure or admission to the intensive care unit (113,116).

This is important to raise as the ability to express milk early (first hour after birth) is preferable for increased milk production (129) and high intake of breast milk during the first postnatal week is associated with exclusive breastfeeding at 36 weeks PMA in infants born between 23- 31 weeks GA (130).

Other non-clinical factors that might affect the establishment of breastfeeding due to maternal factors are mothers' sociodemographic and cultural factors ( i.e maternal age, parity, race, education level, paid/unpaid maternity leave) (113,131,132), previous breastfeeding experiences and support from partner and family (133) as well as mother's intention to breastfeed (134). Furthermore, in the challenging and stressful environment in neonatal units, the mother's tiredness and anxiety during an infant's hospitalisation can negatively affect lactogenesis (135) and leads to reductions in the maternal breast milk supply (136).

These highlights the importance of providing maternal education and a conducive environment in the unit to support breastfeeding. Healthcare factors such as hospital staffing, staff attitudes and support towards breastfeeding, availability of guidelines, and design of neonatal units are among the important factors in determining the successful establishment of breastfeeding culture in neonatal units (137,138). In addition, a systematic review on barriers of breast milk feeding in the NICU from a parent perspective revealed that education on breastfeeding, being supportive for mothers to breastfeed and being adaptive towards the needs of the parents and NICU procedures were associated with successful breastfeeding (136).

Accordingly, current guidelines available for the support and promotion of breastfeeding in neonatal units include staff training, education on benefits and challenges of breast milk and breastfeeding, avoiding or minimising mother-infant separation, promoting kangaroo care/skin-to-skin contact, support for early breast milk expression and easy access to breast pumps (139–143). Furthermore, the implementation of the Baby-Friendly Hospital Initiative (BFHI) or neo-BFHI (141) is also a plausible intervention that could improve breastfeeding prevalence in neonatal units.

Therefore, parents need to have adequate information on what to expect when infants were admitted to neonatal units and early education on breastfeeding establishment is very crucial. At the same time, neonatal units as the healthcare provider should have appropriate training required for the nursing staff as well as a breastfeeding policy in place to provide a supportive environment for the successful initiation and sustaining of breastfeeding among sick and preterm infants. It has been proposed that even small changes in the prevalence of breastfeeding may result in significant health benefits for infants and mothers as well as positive changes in healthcare costs in general (144).

### 1.4.4 Growth assessment

In the assessment of the growth of an infant, the Z-score system is often used and regarded as the best system in the analysis and presentation of anthropometric data (145). It conveys anthropometric values such as weight, length, or head circumference for age as a number of standard deviations (SDs) below, or above, the reference population mean or median value (145). This can be expressed in a form of weight-for-age Z-scores (WAZ), length-for-age Z-scores (LAZ) and head

circumference-for-age Z-scores. These Z-score summary statistics are useful for the classification of growth data by age/gestational age and sex.

The summary statistics can be compared with the reference chart used, which has an expected mean Z-score of 0 and an SD of 1.0 for all normalised growth indicators (145). A negative Z-score change suggests a decline in growth status, a positive Z-score change indicates an increase or improvement in growth status, while a Z-score change of zero shows a stable or unchanged growth status (146). Therefore, the use of change in Z-score, rather than a Z-score alone, is desirable to assess the effect of any interventions i.e. nutrition on growth (145). There is also other way in analysing growth, such as the use of conditional growth modelling, which analyses the effect of weight and height gain by regressing current weight/length on birthweight and earlier measures of weight/length, to derive standardised residuals. This indicates how an infant deviate from its expected weight/length, based on its previous measures and the growth of studied population, in which a positive value represents a weight gain, or faster growth than predicted (147).

SGA is most commonly defined as less than the 10th percentile of weight for GA (or WAZ below -1.28) on specified reference growth chart while AGA is the weight for GA between 10th to 90th percentile (or WAZ between -1.28 and 1.28), and LGA (large for gestational age) is when weight for GA at >90th percentile (WAZ of >1.28) (148). In comparison to SGA, IUGR is defined as a condition triggered by a clinical or pathological process that causes weight to be less than the estimated weight (149). This can also be detected when there is diminished growth velocity documented by at least two intrauterine growth assessments. This condition is most commonly, but not exclusively, diagnosed when an infant has an obvious

intrauterine growth failure with normal head circumference (HC) and/or Doppler velocimetry abnormalities (95).

In various practices in the UK, the US and most Asian countries including Malaysia, the most common growth charts used are the UK-WHO 2011 (Neonatal and Infant Close Monitoring (NICM) Growth Chart**)** and Fenton Preterm Growth Chart 2013 (150,151) (Appendix 1). These charts are used for monitoring the growth of preterm infants from around 23 weeks' PMA and for calculation of Z-scores, directly linked to the WHO post-term growth standard (152). The UK-WHO growth chart may be used to monitor the growth of preterm infants up until 2 years old CGA with the combination of UK 1990 and WHO data. Similarly, the Fenton 2013 growth chart also links to the WHO growth data, but from birth up until 10 weeks post-term.

There is also a recently published chart known as INTERGROWTH-21st Preterm Postnatal Weight Standards (153) (Appendix 1) regarded as a new standard growth chart that has been constructed based on WHO prescriptive approach to match the WHO Child Growth Standards for term infants. The reference data used were from preterm infants in a longitudinal study tracked from the start of healthy and uncomplicated pregnancy to 2 years of age and who were selected carefully as having a low risk of adverse clinical outcomes, no evidence of IUGR and birth anomalies and were cared for according to published recommendations for feeding preterm infants (153,154). However, this chart draws on insufficient data prior to 33 weeks, and small numbers at 33-34 weeks, making it only be a suitable tool for monitoring the growth of preterm infants who are born at ≥32 weeks GA up to 6 months' post-term-CA.

In comparing the Fenton and UK-WHO charts, there are differences for infants below 30 weeks PMA which are possibly due to Fenton's much larger sample size

and more recent data with a better estimation of GA (<30 weeks PMA 12,000 vs. 146 in UK-WHO). There are also differences in term infants at around 38-40 weeks PMA, likely to be due to the statistically smoothing of the Fenton charts as it links to postnatal growth WHO data at around 40 weeks. This was performed to avoid the dip that reflects the slower growth in utero that occurs just prior to term (146). Therefore, for the first study in this thesis on 2.3.7.3 (Chapter 2), the calculation of Z-scores and their reference centiles are based on the Fenton growth chart as this has the advantage of being more recent and covering larger data sets of infants of various ethnic groups from many countries.

## 1.5 Postnatal Growth Studies in Neonatal Units

Amongst the early studies that explored postnatal growth of preterm infants in neonatal units, Lemons et al. (155) reported in 1999 that 99% ELBW and 97% VLBW born between 1995-1996 had growth failure at 36 weeks' PMA. However, although more recent reports in the same cohort of National Institute of Child Health and Human Development Neonatal Research Network (139), in 2010, showed the incidence had decreased, growth failure rates were still high at 79% with a similar trend also reported at another healthcare system (158,159).

However, in 2002, in studying the variation in nutritional practices, especially of the mean caloric and protein intake, Olsen et al. (156) showed that it accounted for the largest difference in growth among the six US NICUs included in the study. This seems to be consistent with the earlier study (160) that also found that better nutritional support is associated with improved growth and less growth failure.

So, does this mean that postnatal growth failure could be improved with better nutritional care? Recently, a lot of efforts have been made to develop and

implement guidelines, internationally or even locally with the development of protocols in NICUs, specifically for the nutritional care that aims to optimise the growth of preterm infants (161–164).

However, a retrospective cohort study in 2015 showed that half of the VLBW preterm infants from the NICUs from the Vermont Oxford Network were still categorised as having “postnatal growth failure” or “severe growth failure,” despite receiving high-quality care and better nutrition therapy (158). This is supported by other retrospective cohort studies involving very low birthweight infants at GA of 22-32 weeks who were born between 2005 and 2012 and at another hospital network, extremely low GA (22-28 weeks) and VLBW (401-1500 g) who were born at between 2003 and 2007. These studies reported that even with the advancements in evidence-based nutritional interventions over 20 years and the current focus on “early aggressive nutrition” in NICUs, undernutrition and postnatal growth failure remain significant problems for preterm infants (157,159).

On a contrary, in a study by Santerre et al. (41), there was an improvement in the WAZ in the first 6 weeks of life for infants with decreased cumulative protein deficits as a result of the optimised nutritional protocol. Additionally, another study that investigated the change in growth after implementation of a new nutrition policy (39) found that infants who were admitted after the policy change to give higher protein intakes had a significantly lesser change in Z-score between birth to discharge for the weight (0.0 (1.2) vs −0.9 (1.1), p=0.001), length (−0.8 (0.8) vs −1.2 (1.1), p=0.02) and head circumference (−0.2 (1.1) vs −1.1 (1.6), p<0.001).

This is also supported by a recent longitudinal cohort study (42) which showed no weight loss for all gestational age groups after enhanced nutritional strategies were introduced in the units with a mean change in WAZ between birth and 36 weeks of

−0.27 (95% CI −0.39 to −0.15). Overall, only 11% of infants in the study had postnatal growth failure at 37 weeks PMA. However, the study contained a considerable number of SGA infants who arguably might show a catch-up growth, which could be the confounding factor. Furthermore, there were also centile lags for head circumference and length across many groups that might indicate disproportionate growth of the infants studied.

In terms of body composition, an earlier study (165) showed that the mean (SD) percentage of fat mass in preterm infants at term-corrected age was significantly higher as compared to term infants (14.8 (4.4) vs 8.59 (3.71), $p<0.0001$), and the fat mass was negatively correlated with gestational age ($p<0.001$), but positively associated with an increase in weight ($p<0.05$). To look into the effects of different types of milk feeding, in a UK study (166) which compared the exclusive breast milk feeding (100% BM) infants with predominantly formula-fed infants (BM ≤ 50%), the latter group had greater weight and more non-adipose tissue mass at term and a greater positive WAZ change between birth and term but no significant differences in weight, non-adipose tissue mass and change in WAZ between the exclusive breast milk and predominantly breast milk (BM 51%-99%) groups. The slower weight gain observed in preterm infants fed with breast milk was postulated to be due to a deficit in non-adipose tissue mass which may reflect lower protein intake among these infants.

These numerous works performed investigating the effects of various feeding strategies on growth outcomes are still producing conflicting results with different study designs and different groups of preterm infants. However, these differences in feeding practices and their impacts on growth outcomes between neonatal units possibly indicate that there may be potential to improve growth with better nutritional practices, although evidence from definitive and larger studies are still needed.

Other than nutritional practices, medical conditions could also affect the growth of preterm infants in neonatal units. One of the most common medical condition, which also impacts the way feeding is being implemented is gastro-oesophageal reflux (GOR) or known as gastro-oesophageal reflux disease (GORD) if it presents with complications. Various studies show that preterm infants who were diagnosed with GORD have longer hospital stays (167–169) and higher hospital costs than infants without GORD making it an important clinical phenomenon in neonatal units (170). The next section will discuss GORD and the management of GORD among preterm infants in neonatal units.

## 1.6 Gastro-Oesophageal Reflux Disease (GORD) among Preterm Infants

### 1.6.1 Definition and prevalence

According to the current clinical practice guidelines for the diagnosis and management of reflux in the paediatric population from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and ESPGHAN combined (NASPGHAN-ESPGHAN 2018) (171), GOR is defined as the "passage of gastric contents into the oesophagus with, or without, regurgitation and vomiting". This is considered as a normal physiologic process occurring several times per day in healthy infants due to intakes of pure liquid diet and supine posture, making it more frequent in infants especially among preterm infants (172,173).

These recurring episodes of GOR also might generally present at two to three weeks of age and usually show improvement around 6 months of age with self-resolution by around 12 months old. This is consistent with progression to a more solid diet and upright posture during food consumption (173,174). However, physiologic GOR can deteriorate to cause GORD when the reflux of gastric contents into the oesophagus causes problematic symptoms and/or complications that affect daily functioning or cause complications such as oesophagitis or stricture (171,172).

The true prevalence of GORD in infants and, specifically, preterm infants is still unknown. However, few paediatric surveys and cohort studies are available as a guide for estimation. In the UK, a cohort study of children and adolescents aged 1–

17 years using data extracted from The Health Improvement Network (THIN) (175) database between 2000-2005 showed that the incidence of GORD among 1 year-olds was 1.48 per 1000 person-years (95% CI: 1.27–1.73) and the overall prevalence during the whole study period was 1.25% (95% CI: 1.22–1.28%), but 55% of the GORD cohort were adolescents (aged 12–17 years).

In other countries, estimated GORD diagnosis rates across neonatal units in the US using symptoms-based prevalence showed an average of 10%–40% (170,176), 22% in Australia (177) and 23.1% in Italy (178). In another review, the prevalence of GORD in infants was estimated to be 2.2-12.6% for infants between 0-23 months, but with no further details by geographical regions (173).

### 1.6.2 Pathology

A few mechanisms have been postulated as possible pathways in causing GORD among infants. The most important one is transient lower oesophageal sphincter relaxation (TLESR), which causes a sudden drop in lower oesophageal sphincter (LES) pressure to levels at, or below, intragastric pressure (179). This causes regurgitation of stomach contents into the oesophagus that is unrelated to the swallowing process.

Expectedly, preterm and LBW infants are understood to be at particularly high risk of developing GORD due to the immaturity of this sphincter and impaired oesophageal peristalsis. Furthermore, although it was shown that the frequency of TSELR is the same in preterm infants regardless of an association of GORD or not, infants with GORD are more likely to experience acid regurgitation during LES relaxation than those without GORD (180). This was also found to occur in many

age groups, and even in less mature preterm infants as early as 26 weeks gestation.

Other factors related to preterm infants' risk of GORD are relatively abundant milk intake, milk protein allergy, the use of feeding tubes, supine and right lateral body positions as well as other complications due to prematurity such as apnoea, BPD, hypoxic-ischemic encephalopathy, intraventricular haemorrhage (IVH) and neurologic impairment (179).

### 1.6.3 Diagnosis and treatment of GORD for preterm infants

In general, distinguishing physiologic GOR and GORD is challenging. Among the common symptoms related to GORD in infants are excessive crying, frequent regurgitation/vomit or posseting, irritability and back arching. However, these symptoms occur even in healthy infants, and there is also no evidence that these symptoms are temporally associated with GOR events (181–183).

In addition, GORD might also be linked with a few other respiratory, gastrointestinal, and neurobehavioral signs such as wheezing, apnoea, episodes of oxygen desaturation, aspiration pneumonia, swallowing dysfunction, disorganised and dysfunctional sucking or swallowing which, in turn, might lead to lower energy intake leading to weight loss as well as feeding difficulties (172).

A recent guideline by NASPGHAN-ESPGHAN (2018) has compiled a list of symptoms and signs that might be indicative of GORD for infants and children 0-18 years old (Table 1.3) together with a number of gastrointestinal and systemic manifestations, that might be the 'red flags' (Table 1.4) that suggest possible other

illness apart from GORD in the infant presenting with regurgitation and/or vomiting symptoms.

**Table 1.3: Signs and symptoms associated with GORD in infants and children 0-18 years old**

| SYMPTOMS | SIGNS |
|---|---|
| **General** | |
| Discomfort/irritability (Unlikely to be related to GORD if single event).<br>Failure to thrive<br>Feeding refusal<br>Dystonic neck posturing (Sandifer syndrome) | Dental erosion<br>Anaemia |
| **Gastrointestinal** | |
| Recurrent regurgitation with/without vomiting in the older child<br>Heartburn/chest pain (typical in older children)<br>Epigastric pain (typical in older children)<br>Hematemesis<br>Dysphagia/odynophagia | Oesophagitis<br>Oesophageal stricture<br>Barrett oesophagus |
| **Airway** | |
| Wheezing<br>Stridor<br>Cough<br>Hoarseness | Apnoea<br>Asthma<br>Recurrent pneumonia with aspiration<br>Recurrent otitis media |

The table is adapted from (171)

**Table 1.4: Common alarm signs and symptoms suggestive of differential diagnoses to GORD**

| SYMPTOMS AND SIGNS | REMARKS |
|---|---|
| **General** | |
| Weight loss | May suggest condition such as systemic infection |
| Lethargy | |
| Fever | |
| Excessive irritability/pain | |
| Onset of regurgitation >6 months or increasing/persisting >12 - 18 months of age | Late onset as well as symptoms increasing or persisting after infancy, based on natural course of the disease, may indicate a diagnosis other than GORD |
| **Gastrointestinal** | |
| Persistent forceful vomiting | Indicative of hypertrophic pyloric stenosis (infants up to 2 years old) |
| Nocturnal vomiting | May suggest increased intracranial pressure |
| Bilious vomiting | Indicated for symptom of intestinal obstruction. |
| Haematemesis | Suggest a potentially serious bleed from the oesophagus, stomach or upper gut |
| Chronic diarrhoea | May suggest food protein-induced gastroenteropathy |
| Rectal bleeding | Indicative of conditions such as bacterial gastroenteritis and inflammatory bowel disease |
| Abdominal distension | Indicative of obstruction, dysmotility, or anatomic abnormalities |

The table is adapted from (171)

#### 1.6.3.1 Nonpharmacologic therapies

In the case of an infant with uncomplicated GOR, a thorough history and physical examination should suffice in establishing a clinical diagnosis after excluding other possible diagnoses. The history should include the GA, symptom initiation, a feeding history such as duration of the feeding period, feeding volume, type of milk feeds, feeding interval and frequency, the pattern of regurgitation, a family medical history, possible environmental risk factors such as parental tobacco use, the patient's growth records, prior medications and the presence of red flags or warning signs (171).

If further action is needed, the initial treatment should be conservative and managed in a stepwise manner which usually includes changes in feeding practices and/or parental education and counselling, especially for infants who only had physiologic GOR (180). However, there is a lack of evidence to support changes in feeding practices for preterm infants although common strategies include the use of feed thickener and offering smaller, more frequent, feeds. Commonly used feed thickeners are cereal-based and produced from rice or maize, gum-based thickeners from guar /locust bean, and carboxymethyl cellulose (184). They may act by causing the liquid to be more adhesive to hold the feed in the stomach, which is advantageous. On the contrary, they may worsen GOR by increasing the energy density and osmolarity of feeds, causing an increase in the frequency of LES relaxation and a delay in gastric emptying (174,184).

In addition, there were also some controversial products of thickener (SimplyThick – xanthan gam-based) linked to an incidence of NEC for which the US Food and Drugs Administration (FDA) has warned against its use (185). Meanwhile, other commercially available formula products that thicken on acidification in the stomach

such as starch-thickened preterm formula are not nutritionally appropriate for preterm infants (171). Furthermore, a systematic review of RCTs of thickened formulas in term infants with GOR, highlighted that these formulas were only able to reduce the regurgitation episodes but ineffective in reducing acidic GOR (186).

In addition, feeding intervention such as trying for smaller but more frequent feedings results in decreased GOR events but also shows more frequent acidic reflux episodes (187). This is in agreement with another study which also demonstrated decreased GOR episodes with longer feeding duration and slower milk flow rates, although the nutrient composition of expressed breast milk, especially the energy content, may be compromised with longer feeding time due to fat loss from the continuous feeding (188).

Another strategy suggested was to change the normal feeding tube position to be in the jejunum or “transpyloric” position. In theory, this means that enteral feeds will reach the main sites of nutrient absorption which could have the advantage of decreasing the potential for GOR, reflux-associated apnoea or bradycardia, and aspiration pneumonia (189). However, meta-analyses (189) showed that this relocation did not lead to any advantage to the infant’s growth or feeding tolerance, but instead, an increased incidence of gastrointestinal disturbance and possibly mortality were reported (typical RR 1.48 (95% confidence interval (CI) 1.05 to 2.09); typical RD 0.09 (95% CI 0.02 to 0.17); number needed to treat for an additional harmful outcome (NNTH) 10 (95% CI 6 to 50); six studies, 245 infants) and all-case mortality (typical RR 2.46 (95% CI 1.36 to 4.46); typical RD 0.16 (95% CI 0.07 to 0.26); NNTH 6 (95% CI 4 to 14); six studies, 217 infants). However, the results might be affected by the selective allocation of the less mature and sicker infants to transpyloric feeding in the trial that contributed the most weight to these outcomes (189).

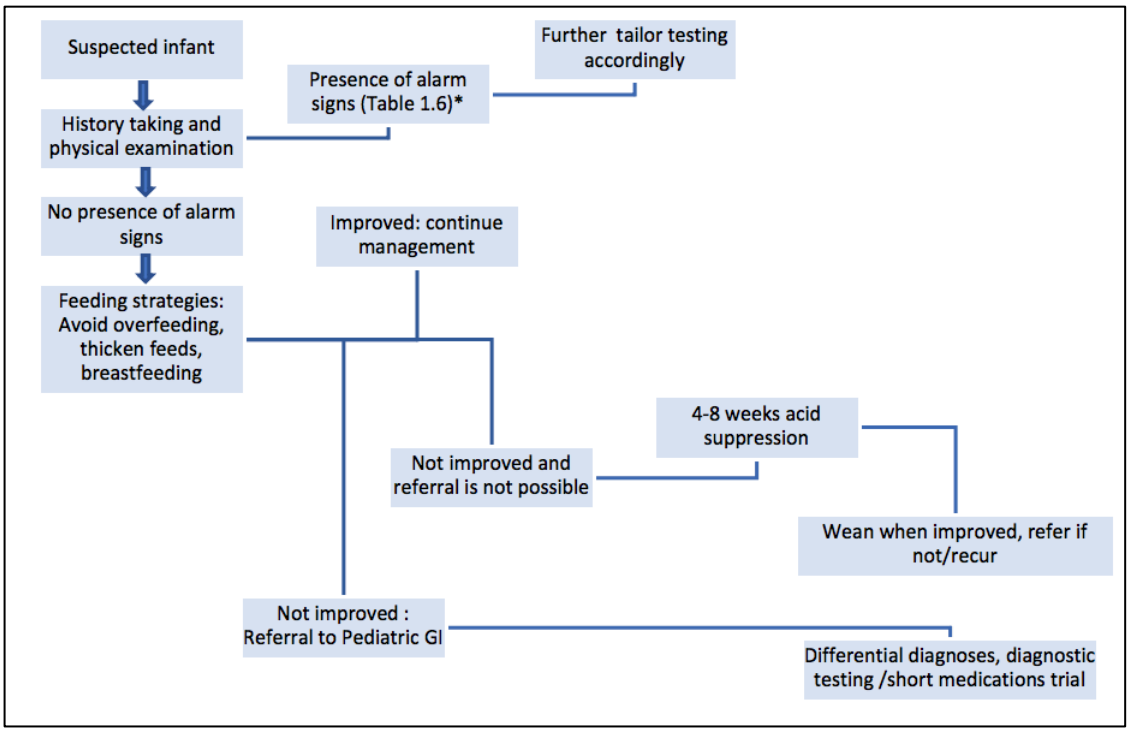
There is also a recommendation to change infant's milk to elemental or extensively hydrolysed protein formulas (eHPF), as studies showed that the use of an eHPF improved GOR symptoms in infants with suspected GOR (190), while in preterm infants, it significantly reduced the number of GORs detected by pH monitoring ($p= 0.036$) and also the reflux index ($p = 0.044$) when compared to the standard preterm formula (211). However, this is not a better option for breast-fed infants as it might encourage the switching to formula feeding. Moreover, the findings did not exclude possibilities of overlap between signs of cow milk protein allergy and those symptoms attributed to GOR, including vomiting, failure to thrive, and irritability (191,192).

Therefore, for non-pharmacological feeding strategies, the current NASPGHAN-ESPGHAN guideline proposes to use a feed thickener for treating visible regurgitation/vomiting in infants with GORD due to some evidence of the improved occurrence of these symptoms, although there are uncertain side effects in its use (171). Modifications of feeding volumes and feeding frequency are also suggested, as these changes are without risk or cost as compared to other costly or risky interventions. This should be adjusted according to age and weight to avoid overfeeding in infants with GORD (171). In addition, a 2-to-4-week trial of formula with eHPF (or amino-acid based formula) in formula-fed infants has been suggested to the suspected case of GORD when other non-pharmacological treatments have been unsuccessful (171).

For body positioning strategies, studies showed that placing preterm infants in the left lateral, versus right lateral, position after feeding and in prone, versus supine, the position may reduce TLESRs and reflux episodes (187,193). However, in a

study of term infants, behavioural signs of GOR such as crying and/or irritability did not improve despite a reduction in reflux episodes with the left lateral position (194).

Furthermore, the AAP, NASPGHAN, the UK National Health Service (NHS) and other national bodies advise that infants with GOR should lie in the supine position, except for infants whom the risk of death from GOR is greater than the risk of Sudden Infant Death Syndrome (SIDS) (195). Studies in term and older infants have shown that elevation of the head is not advantageous in reducing GOR (196), but it is still inconclusive for preterm infants. Figure 1.2 shows the NASPGHAN-ESPGHAN recommendation flowchart for managing infants with suspected GORD which includes non-pharmacological therapies.




In an infant with recurrent regurgitation/vomiting, a detailed history and physical assessment with consideration to warning signals suggesting other diagnoses is generally sufficient to establish a clinical diagnosis of uncomplicated infant GOR. Figure adapted from (171).

**Figure 1.2: Management algorithm for infants with frequent regurgitation**

As shown in Figure 1.2, diagnostic testing for GORD is suggested as the last step after other conservative treatments do not work i.e. have not improved symptoms. However, some neonatal units do earlier diagnostic testing for infants with significant GOR, or suspected GORD, using methods such as pH monitoring, multichannel intraoesophageal impedance (MII) monitoring, contrast fluoroscopy, endoscopy and biopsy (197), although the use and effectiveness of these in preterm infants are unclear.

Lastly, some clinicians use a trial of pharmacologic intervention as diagnostic testing for GORD and these usually involve the use of an acid suppression drug. This is also suggested by the current NASPGHAN-ESPGHAN guidelines to offer acid suppression for 4-8 weeks if nonpharmacologic measures were unsuccessful or when there is a strong clinical suspicion that GOR is causing complications (Figure 1.2). These time-limited trials are, however, not conclusive of a diagnosis as the unclear symptoms associated with GOR and the possibility of symptom improvements due to increasing age or maturity. This recommendation however not specifically clear about applicability to preterm infants or infants in neonatal units. This group of infants might present with troublesome or differential signs and symptoms that are suspected to be due to GORD. Therefore, suspicious cases should be evaluated thoroughly (179).

Additionally, the current NASPGHAN-ESPGHAN guidelines state that a short trial of a PPI is not recommended as a diagnostic test for infants (171), possibly due to findings from five RCTs of using proton pump inhibitors (PPIs) in preterm and full-term infants for 2 – 4 weeks treatment period that showed no symptom reduction over placebo (198).

### 1.6.3.2 Pharmacological therapies

**Histamine-2 Receptor Antagonist**

With the correct dosage, H2RAs are effective in the treatment of peptic disease and healing erosive oesophagitis, at least in adults. However, prolonged use would lead to rapid tachyphylaxis and ineffectiveness (173).

In preterm infants, a few studies have shown that H2RA use may predispose infants to a higher incidence of infections, NEC and death (199–201). The increased risk of infections has been postulated to results from the drug's action in inhibiting gastric acid secretion which i) increases the pH – leading to the alteration of the intestinal microbiome, ii) increases the production of pro-inflammatory cytokines, and iii) decreases immunological response to infection (184,181). This condition, known as gastric hypochlorhydria, may allow bacterial survival, favouring gut colonisation and potentially leading to bacterial overgrowth, which is known to play an important role in the pathogenesis of NEC.

A systematic review and meta-analysis performed to test the association between H2RA and adverse outcomes in neonates (203), showed that in three cohort studies (200,204,205), there was an association between NEC and H2RA (unadjusted analyses' pooled OR: 2.60; 95% CI: 1.58-4.28, P =0.0002). Similarly, the adjusted analyses including one cohort and two case-control studies (201,206,207) also demonstrated an association between H2RA and NEC (pooled OR: 2.81; 95%CI: 1.19–6.64; p=0.02).

For infections, a collective review of results from seven studies (200–202,205,208–210) showed that 17% of infants who were exposed to H2RA had infections as compared to 7.2% of those not exposed to H2RA, resulting in an unadjusted pooled

OR of 3.38 (95%CI: 1.92–5.94; p <0.001). Likewise, the adjusted value of pooled OR for two studies (210,211) was 2.09 (95% CI: 1.35–3.24; p<0.001). Specifically for sepsis, pneumonia and urinary tract infections, the associations were found based on the respective unadjusted pooled OR of 2.75 (95% CI: 1.51–5.02; p=0.001) for sepsis in five studies (200,201,205,208,209) and OR of 2.93 (95% CI: 1.45–5.92; p=0.003) and 8.73 (95%CI: 2.38–31.98; p=0.001) for pneumonia and urinary tract infections from three studies (201,205,209).

In the UK and many other countries, this medication is currently unlicensed to use for patients below 3 years old (oral medications) and below 6 months old (injections) (212).

**Proton Pump Inhibitors**

A study conducted by Omari et al. (213) showed that omeprazole is effective in reducing the frequency of acid reflux episodes and the overall degree of oesophageal acid exposure in premature infants. However, the number of symptomatic events such as vomiting, apnoea, bradycardia, choking, behavioural changes were not significantly improved.

Similarly, in the study by Moore et.al (214), omeprazole significantly reduced the reflux index as compared to placebo, but irritability improved regardless of treatment. This is consistent with other studies in infants that found no significant advantage of PPIs (lansoprazole and esomeprazole) in treating symptoms attributed to GOR (215). In another study, lansoprazole was associated with a higher rate of adverse events, particularly lower respiratory tract infections, compared with the placebo group (10 vs 2; p= 0.032)(216).

More studies of adverse effects associated with PPI use are available that mostly includes older children. However, data on the efficacy of PPIs in the preterm population are still scarce and most evidence on the adverse effects such as NEC and infections were jointly concerning both PPIs and H2RA (217). For example, a study (204) showed that children (median age (IQR) of 10 (8-16) months) in two groups who were treated with omeprazole/ranitidine for two months had significant increases in acute gastroenteritis and community-acquired pneumonia compared with healthy controls during the four-month follow-up period. No differences were seen between H2RA and PPI users in both incidences of acute gastroenteritis and pneumonia in the previous 4 months and during the follow-up period.

In addition, many studies showed higher risks of infection with Clostridium difficile among children exposed to PPIs (218–221). Additionally, there have been reports of increased risk of fractures, hypomagnesemia, dementia, myocardial infarction, and renal disease in association with PPI in adult studies, but no strong evidence has been shown for either paediatric populations or preterm infants to date (171,222).

However, given these worrying trends in studies demonstrating side effects of PPIs in adults, it is recommended that these medications must be prescribed only when there is a clear diagnosis of GORD, with the lowest doses and shortest duration as appropriate.

Both prescriptions of H2RAs or PPIs in infants however are not approved by the FDA, except for short-term use of esomeprazole, omeprazole, and famotidine for infants one month and older with a diagnosis of erosive oesophagitis (180). The current NASPGHAN-ESPGHAN guideline also mentions that these medications should not be used for infants with “uncomplicated” GOR that presents with common signs such as crying, distress, and visible regurgitation (171).

In the UK, the National Institute for Health and Care Excellence (NICE) – British National Formulary (BNF) for children states that “acid-suppressing drugs, such as PPI or H2RA should not be used to treat regurgitation in children occurring as an isolated symptom” (223). However, it also states that a 4-week trial of a PPI or H2RA could be an option for patients who are unable to talk about their symptoms (i.e. infants and young children, and those with neurodisability/communication difficulties) who have overt regurgitation with one or more of the following conditions: i) unexplained feeding difficulties (for example, refusing feeds, gagging or choking) ii) distressing behaviour, or iii) faltering growth. Response to such a trial of treatment should be assessed and referral to a specialist for possible endoscopy if the symptoms do not resolve or recur considered (223).

On another note, in choosing H2RA or PPI for treatment, NASPGHAN-ESPGHAN guideline recommends PPIs as the first-line treatment for the reflux-related erosive oesophagitis in infants and children with GORD (171) (no specificity for preterm infants) and H2RAs as a second-line therapy in the treatment of oesophagitis caused by acid reflux when PPIs are not available. The choice of PPIs or H2RA, however, depends on availability (based on age), cost and other practical considerations as no evidence support the advantage of PPI or H2RA over another.

**Sodium Alginate**

A combination of sodium bicarbonate and alginate formulations work in the presence of acid by precipitating into a viscous gel that acts as a physical barrier to the gastric mucosa, protecting the lower oesophagus from acidification. A small study undertaken in preterm infants showed that this formulation decreased the number of acidic GOR episodes, total oesophageal acid exposure and the frequency of regurgitation events (224,225). This is consistent with the other study

(226) that found a significant decrease in the number of infants regurgitating when treated with alginates when compared with no intervention (RR = 0.04, 95% CI 0.01 – 0.25) or with thickened feeds (RR = 0.26, 95% CI 0.26 – 0.88).

In other studies, significantly lower numbers of vomiting/regurgitation episodes were also demonstrated when compared to placebo (227), while improved crying-fussiness, cough episodes as well as decreased acid and non-acid GOR episodes measured with pH-impedance recording were shown in another study (192). However, because it is still uncertain if the use of this formulation could lead to any possible side effects in preterm infants, it is suggested that their use for chronic treatment of infants and children with GORD is avoided (171,228).

**Prokinetic Agents**

Prokinetics are an antidopaminergic agent that could improve gastric emptying, reduce regurgitation, and enhance LES tone. Although these agents, which include metoclopramide, domperidone, and erythromycin have been widely used in older infants to reduce the symptoms of GOR, none of these drugs has been shown to reduce GOR symptoms in preterm infants (197,229).

Moreover, prokinetic agents have significant side effects which include a higher risk of infantile pyloric stenosis (erythromycin), cardiac arrhythmia (erythromycin), and neurologic side effects (domperidone and metoclopramide) (230,231). Studies also show that the therapeutic dosage of metoclopramide is very close to the toxic dosage resulting in a very narrow safe dosing range. The FDA issued a warning in 2009 declaring that use of this agent for infants <12 months old was contraindicated due to its adverse effects, while in 2013 the European Medicines Agency (EMA)

also released a statement regarding the risk of neurological adverse effects of metoclopramide with prolonged use and high dosage (171).

In addition, in December 2019, The National Institute for Health and Care Excellence (NICE) (212,223) announced that domperidone (in addition to metoclopramide and erythromycin) is no longer licensed for use in children younger than 12 years or those weighing less than 35 kg. This is due to lack of evidence for benefit and following European restrictions issued in 2014 confirming the risk of serious cardiac adverse drug reactions such as serious ventricular arrhythmia and sudden cardiac death.

## 1.7 The Management of GORD and Use of Anti-Reflux Medications in Neonatal Units: current perspectives

### 1.7.1 GORD diagnosis

In the management of GORD among preterm infants, there are a lot of ‘grey’ areas that have not been identified clearly. These include diagnostic criteria, “troublesome” signs and symptoms as well as the indications for use of pharmacological treatment. Determination of the exact prevalence of GOR versus GORD is also challenging because there is an unclear distinction between physiologic and pathologic reflux. Additionally, the terms “reflux”, “acid-reflux”, and GORD are often used interchangeably by healthcare professionals as well parents and families of the infants (212). In a systematic review of interventions for GORD, out of 26 studies included, there were 25 different ways of defining reflux and 21 studies used a unique definition of GORD (232).

In determining GORD diagnosis in infants, the Infant-GER-Questionnaire-Revised (IGERQR) score which is based on a parent/provider perception for the 12-symptom based domains has been used and validated in many hospitals, but is yet to be proven for use for NICU infants (233,234). However, it is difficult to diagnose GORD based on the symptoms score for those infants in NICU, particularly as preterm infants often present with many prematurity-related conditions that could be all be erroneously attributed to GORD. The uncertainties in GORD symptoms and management among preterm infants has been postulated to cause overdiagnosis and overprescribing medications in neonatal units, even among healthy infants with physiologic GOR (216,235).

For example, in a retrospective cohort study of 33 neonatal units in the USA (170), there was a wide variation between the units in the proportion of preterm infants who received a diagnosis of GORD recorded based on the International Classification of Diseases, Ninth Revision (ICD-9) code 530.81. Approximately 10% of infants (n=18567) of 22 to 36 weeks GA and >400g birth weight were recorded to have GORD (95% confidence interval [CI]: 9.8–10.7) with rates ranging from 2.4% to 29.9% ($p< 0.001$) across the NICUs. This significant variation in the prevalence of GORD among NICUs, however, raised issues over whether this reflects variability in the diagnostic criteria or GORD testing used, rather than the variation of the true prevalence of pathologic GORD.

However, even with such uncertainties, coupled with the lack of evidence for the efficacy and increasing safety concerns of anti-reflux medications for infants, there is still a concerning high and increasing prescription use during hospital admission (236–238), as well as after hospital discharge (221).

### 1.7.2 Use of Anti-reflux Medications in Neonatal Units

In the US, a large retrospective study involving infants admitted to NICUs in 43 children's hospitals (n=122002) (240) reported that approximately 24% of these infants received either an H2RA or PPI. Among infants born at ≤24 weeks GA, 29% had H2RA use and 18% used PPIs, while among those born at 26–36 weeks GA, 28% were treated with H2RA and 20% with PPI. In this cohort, 11.2% of infants had recorded an ICD-9 diagnosis of GORD and 74% of them have been treated with either an H2RA or PPI, while 54% and 47% have received either an H2RA or PPI, respectively. The majority (56%) of treated infants were also reported to be receiving either H2RA/PPI at discharge, possibly reflecting the over-prescription of anti-reflux medication.

In another study involving ELBW infants (22-34 weeks GA) enrolled in the National Institute of Child Health and Human Development Neonatal Network generic database from 2002 to 2003 (n=1598) (239), approximately 25% were discharged from the hospital with anti-reflux medications. Additionally, a higher proportion of infants were prescribed anti-reflux medications at discharge if they were discharged after 42 weeks PMA (48%) as compared to infants who were discharged before 42 weeks PMA (19%). This might indicate the interference of the GOR symptoms on the well-being of the infants during admission which prolong hospitalisation, or they might also have other conditions that lengthen their hospital stay such as GI-related surgeries which are more likely to expose them to have GORD and being prescribed with the medications.

In the UK, a survey of consultants from 57 major level II and III NICUs (241) reported that 46% of responding units used medications for GORD treatment. For the medications used, all of these units reported the use of H2RA, 98% used feed

thickeners, 97% used antacids, 79% used prokinetic agents, and 65% of the units used PPIs. The most common feed thickeners used were Carobel® (55%), Thick and Easy® (40%) and Gaviscon® (26%). Moreover, of 48 units that reported their diagnostic criteria for GORD, 42% made the diagnosis based on clinical signs/symptoms alone such as vomiting, posseting, feed intolerance, and regurgitation (71%), apnoea (69%) and bradycardia (48%). Additionally, when further investigations were performed for a diagnosis, 93% of these units had intra-oesophageal pH monitoring (pHmetry) as the most common method, but it was used regularly in only 30% of the units.

However, in the recent survey which explored current practice in investigation and management of GORD involving 207 neonatal units of all levels in the UK (84% response rate) (242), 32% of units reported always starting medication without investigation with 60% of units reporting use of Gaviscon®, followed by the H2RA, Ranitidine (53%), other feed thickeners (27%), PPI (23%) and prokinetics (28%). Interestingly, the most common method used to confirm a diagnosis was a trial of therapy (58% of units), followed by pH studies (24%), upper GI contrast studies (23%) and multichannel intraluminal impedance (MII)/pH studies (6%).

With more than a decade of difference between these two studies in the UK (2004 vs 2017), it seems like H2RAs, such as ranitidine, are still used frequently in neonatal units, but the use of Gaviscon® has also been more preferred over the years, possibly due to lack of reported side effects as compared to H2RA, PPIs and prokinetics (243). However, even with insufficient evidence to support the use of domperidone and erythromycin, as well as their association with adverse effects such as cardiac arrhythmias (244) and hypertrophic pyloric stenosis (245), respectively, they were still used in 22% and 6% of these UK neonatal units (241,242).

Therefore, there must be a clear understanding amongst health practitioners of any current evidence indicating the rationale for anti-reflux medication prescriptions, especially in preterm infants. The choice of treatment ultimately lies with the health practitioners based on their clinical judgement to consider which therapy to start or which symptoms are considered sufficiently suspicious of GORD.

However, as studies showing ways of managing GORD among infants are largely variable even with the emergence of guidelines, this might indicate the limited awareness in the updated practice guidance, lack of compliance in clinical practice or even limited availability of diagnostic facilities in certain neonatal units or outpatient facilities. Both health practitioners and parents should be well-informed on what are normal physiologic GOR and infant behaviours and understand the limitations of medical therapy in treating GORD.  Furthermore, providing the latest information in parental education and guidance on GORD-related diagnostic and treatment options, side-effects, complications, prognosis and support is highly recommended as part of the treatment of GORD in preterm infants.

## 1.8 Overview of the thesis

### 1.8.1 Rationale of the thesis

Nutritional care practices between neonatal units are highly variable. Effects of these variabilities in feeding practices on growth outcomes among preterm infants are usually observed in single neonatal units or retrospective studies. Even with 'aggressive' nutritional practices, many preterm infants were reported to have growth failure at discharge, while some were reported to have improved, suggesting contradicting outcomes in many neonatal units. This is concerning as it is known that preterm birth and preterm birth complications contribute the most to the rate of neonatal mortality. Neonatal Mortality Rate (NMR), which is the probability of dying during the first 28 days of life is high in most South East Asian (SEA) countries (246). Malaysia, categorised as an upper-middle-income country, as compared to other SEA countries however has the lowest NMR at 5 per 1,000 live birth in 2019, in line with its advancement in neonatal care services, which is comparable to the UK's NMR at 3 per 1,000 live birth, although the rate of preterm birth was reported to increase (247). Additionally, similarly as in the UK, Malaysia's health care system is largely government-funded healthcare, expanded from the system inherited from the British upon independence in 1957 (248,249).

However, in many lower or upper-middle-income countries, as well as in SEA countries, including Malaysia, limited studies have been undertaken on the nutritional practices and growth outcomes of preterm infants in neonatal units. This is despite the growing availability of neonatal intensive care in these settings. A study on nutritional practices and growth outcomes from a neonatal unit in Malaysia was last performed in 2011 (250). Therefore, a study that could demonstrate nutritional practice changes in neonatal units in Malaysia and provide a comparison

with that to a higher-income country such as the UK is highly needed. For this first study, choosing Malaysia as a representative of the upper-middle-income country or SEA country, to compare in terms of feeding practices with the UK would be suitable considering similar healthcare system and NMR value which directly reflects comparable prenatal, intrapartum, and neonatal care with the UK.

In addition, it is uncertain whether wide variation in the feeding practices especially between higher and lower income countries (i.e. low, middle and upper-middle-income countries) would impact the growth of preterm infants differently. For example, in Malaysia, breastfeeding practices are culturally very common, and the recorded rate of breastfeeding is higher as compared to many developed and higher-income countries like the UK or the US (251–253). The use of donor breast milk (DBM), even without an established milk bank, is commonly practised in Malaysia which also involves routine pasteurisation of expressed breast milk in neonatal units in Malaysia (254). In addition, other factors such availability of facilities in neonatal units also differ between countries.

Furthermore, the use of breast milk supplementation such as breast milk fortifier was shown to be high in one Malaysian neonatal unit at c.83% (unpublished data) in 2016 and c.88% in 2011-2012 (255). However, a comparison study among VLBW preterm infants involving two Asian countries including Malaysia showed that even at adequate enteral protein and energy intakes, c.70% of Malaysian infants had postnatal growth failure (PGF) at 36 weeks corrected age with a change in WAZ of >-1 while c.16% had severe PGF with change in WAZ of >-2.

However, in the UK, studies on nutrition intakes and growth outcomes are more frequently performed, using both prospective and retrospective data. In a study involving preterm infants ≤32 weeks GA or ≤1500g birth weight (256), the degree of

PGF was compared at discharge between infants admitted to a level I–II and level III. No differences were found in change in WAZ between the units (level I-II: (−0.46 (0.75) to −1.3 (1.0) vs level III: (−0.46 (0.75) to −1.3 (1.0) and the change in WAZ was lower as compared to the aforementioned Asian studies. Similarly, in the recent study of a single neonatal unit in the UK involving preterm infants <32 weeks GA (42), early postnatal growth failure was shown as inevitable with the introduction of improved nutritional guidelines with the change in WAZ between birth and 36 weeks of −0.27 (95% CI −0.39 to −0.15).

Therefore, there is justification for conducting a study comparing feeding practices and growth outcomes between these countries (Malaysia and UK) of different demographics and settings. It is also valuable to further investigate how the distinct differences in practices such as breast milk use and the use of fortifiers which could translate into diverse intakes of protein could have an impact on the growth outcome at discharge.

During the second year of my study, COVID-19 pandemic started and had affected my access to patients for data collection. As I was unable to conduct further clinical studies in neonatal units, I re-oriented my projects to studies that could be delivered within the limitations imposed by the pandemic restrictions. The studies that I have managed to proceed are discussed below.

In terms of breast milk feeding in neonatal units, factors such as separation of mother and infant and a less supportive neonatal unit staff and environment were among issues identified that may impede the use of breast milk (114). However, since December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has caused a disease called coronavirus or COVID19, has spread worldwide. The WHO on 11 March 2020 (257) declared the pandemic a

public health emergency and, since then, about 6 million cases were detected in the UK with recorded 131000 deaths by 12th August 2021 (258).

In the UK, studies have shown that COVID-19 infection is uncommon among infants admitted to the hospital, even among infants born to infected mothers and possible vertical transmission is also rare (259,260). However, during this pandemic, most hospitals around the world, including in the UK, have employed many immediate health service changes in their neonatal units. These include separation of infants from mothers with suspected or confirmed COVID-19 and even avoidance of any breast milk feeding altogether especially during the early pandemic - although some have revised their position in more recent months (261,262).

Other common recommendations are visiting hours restrictions in neonatal units, complete mothers/infants separation and isolation or room-sharing at a specified distance/time, avoidance of skin-to-skin contact or requiring washing of mothers' chests before skin-to-skin or breastfeeding (263). This is regardless of the WHO's recommendation that women can breastfeed their infants during this time as usual and "mothers should not be separated from their infants unless the mother is too sick to care for her baby" (264). Adverse effects of these changes on breast milk feeding (265) in neonatal units are, therefore, highly anticipated due to the overlapping guidelines (261,262), lack of strong evidence as well as heightened concern and anxiety surrounding this issue among mothers as well as health practitioners (266).

Therefore, a study is needed to investigate if the restrictions imposed during the pandemic might have affected the prevalence of breast milk feeding in the neonatal units. To the best of our knowledge, this is the first study to explore the impact of

COVID-19 restrictions in neonatal units on the rate of breast milk feeding during admission and at discharge.

In neonatal units, GORD is known as one of the medical risk factors identified that may influence feeding, especially among preterm infants. However, reports on the prevalence of GORD in this population are scarce due to the unclear distinction between the pathological reflux from normal physiological reflux. In neonatal units, once preterm infants have become more medically stable and recovered from many prematurity-related acute illnesses, the next important focus would usually be towards feeding practices, nutrition and growth of these infants.

However, some problems, including GORD, which normally become more evident during this time, may disrupt feeding with its associated symptoms such as frequent emesis or regurgitation, feeding aversion, and even exacerbation of chronic lung disease. These associated symptoms might increase the time required for an infant to achieve appropriate weight gain and this can extend infants' stay in the neonatal unit. While NASPGHAN-ESPGHAN clinical practice guidelines have been issued since 2009 (updated in 2018) encouraging non-pharmacological approaches to GORD such as the use of extensively hydrolysed protein formula and thickener before pharmacological therapy, the trend of medications use following the guidelines were unspecified in many countries. Anti-reflux medications have been discouraged for use due to their safety issues related to infections and NEC among preterm infants, however, there is no current data showing the prevalence or trends of use with the emergence of safety studies.

Therefore, a comprehensive study is needed to describe the prevalence of GORD and the use and changes over time of anti-reflux medications in neonatal units in the UK, which could be performed with the use of a large national database such as

the National Neonatal Research Database (NNRD). In addition, a survey study presenting perspectives of health practitioners on their self-reported practices and management of GORD in neonatal units is highly valuable to see if the self-reported practices complement the findings shown in the database study. The views of parents of preterm infants on how their infants' GORD is managed in the unit, and their preferred therapies – which could be pharmacological or non-pharmacological, could also add to the information in improving the management of GORD in neonatal units, taking into consideration the parents' standpoints.

### 1.8.2 Aims and hypotheses of the thesis

1. To describe and compare nutritional practices in feeding preterm infants in two neonatal units in Malaysia and the UK and assess the association between feeding practices and growth outcomes at discharge
   Hypothesis: There are variations in feeding practices and nutritional intakes of infants between the two neonatal units in the UK and Malaysia that impact growth outcomes at discharge.
2. To describe the prevalence of breast milk feeding during admission and at discharge among infants admitted to a neonatal unit in the UK, comparing data before and during the COVID-19 pandemic
   Hypothesis: The prevalence of breast milk feeding during admission and at discharge among infants admitted to a neonatal unit in the UK was lower during the COVID-19 pandemic periods as compared to previous years.
3. To describe patterns of GORD diagnosis and use of anti-reflux medications among preterm infants in England and Wales from 2010-2017
   Hypothesis: The prevalence of GORD is stable over time but the use of anti-reflux medications among preterm infants in England & Wales from 2010-2017 is declining.

4. To explore the current practice and perception of health practitioners on the management of GORD among preterm infants, as well as the perception of the parents of preterm infants on the treatment of GORD received during admission in the neonatal unit.

   Hypothesis: More health care practitioners and parents of preterm infants choose/prefer the use of pharmacological, rather than non-pharmacological approaches in the management of GORD in the neonatal unit.

Therefore, the following studies were designed to achieve these aims.

**Chapter 2: Nutrition and growth of preterm infants in the two neonatal units in the UK and Malaysia**

In this study, a prospective study of feeding practices, nutritional intakes and growth at the discharge of preterm infants in two neonatal units in Malaysia and the UK was performed. Different feeding policies and birth characteristics of infants in these units are expected. These differences were adjusted to explore associations between feeding practices and nutritional intakes and growth outcomes at discharge. This first study provides a cross-sectional overview of current practices and growth status of preterm infants both in two neonatal units in Malaysia and the UK and highlights the importance of improvement of nutritional practices in Malaysia and the UK.

**Chapter 3: Impact of COVID-19 on breast milk feeding during admission and at discharge from UK neonatal units**

In the second study, a retrospective review of the use of breast milk feeding during admission and at discharge among infants admitted to a neonatal unit in the UK will be presented. The prevalence of breast milk feeding during admission and at discharge during the COVID-19 pandemic in which impact of two periods of visiting

restrictions are compared to the pre-pandemic period. These periods of visiting restrictions are i) from 23rd March 2020 to 31st July 2020 in which the restrictions were first implemented and were more constrained, and ii) from 1st August 2020 to 31st December 2020 when the restrictions were gradually relaxed. This study will add to our understanding of the impact of the COVID-19 pandemic, and associated hospital policy and visiting restrictions, on breast milk feeding in neonatal units.

**Chapter 4: Prevalence of GORD and the use of anti-reflux medications among preterm infants in neonatal units in England and Wales from 2010-2017**

For this study, the prevalence of GORD and trends over time in the use of anti-reflux medications and feed thickener prescriptions in neonatal units in England and Wales are described by using the National Neonatal Research Database (NNRD). This study will provide the first, largest overview on the incidence of GORD recorded among preterm infants in neonatal units in England and Wales as well as offering insights on trends in anti-reflux medication use over time.

**Chapter 5: A survey on health practitioners' and parents' perspectives on the management of GORD among preterm infants in the neonatal unit**

This survey undertaken as a patient and public involvement activity (PPI) presented self-reported quantitative and qualitative findings involving i) health practitioners' perspectives on the management of GORD in their respective units, their views on a proposed clinical trial on this area, and ii) parents' perspectives on how their infants are managed for the treatment of GORD in neonatal units and their views on the same proposed clinical trial. This survey is hoped to provide current insights on how GORD is managed in neonatal units as well as presenting clinicians' and parents' perspectives on conducting a clinical trial comparing non-pharmacological and pharmacological approaches used to treat GORD.

## Chapter 6 Conclusion

This chapter will summarise the key findings and overall strengths and limitations of the projects in this thesis. The implications for clinical practice and future research suggestions will be included.

# CHAPTER 2: NUTRITION AND GROWTH OF PRETERM INFANTS AT DISCHARGE

## 2.1 INTRODUCTION

For preterm infants, there are many factors that could interrupt growth and development especially when the infants are subjected to the drastically different extrauterine environmental challenges due to preterm birth. These include their genetic potential, the influence of clinical and feeding practices in the NICU, and medical complications of prematurity (267–269). Of these three factors, the one that can be controlled is clinical and feeding practices in neonatal unit. Optimising feeding interventions may facilitate growth or hinder it, if they are poorly executed.

There are several recommendations that have been made over the years to optimise growth outcomes for preterm infants. These include early and aggressive nutritional strategies in terms of energy and protein intakes, preference for early enteral feeding over prolonged parenteral feeding, early initiation of total enteral feeding, rapid advancement of enteral feed volume, continuous nasogastric feeding as compared to bolus feeding, breast milk use and the use of breast milk fortifier (33,270,271). However, it is uncertain whether these general recommendations can be applied to all where there are complexities in terms of the characteristics of preterm infants studied. In addition, different interpretations of the term ‘postnatal growth failure or retardation’ in published studies (155,272,273) and varied growth outcomes measures used (274,275) present a challenge for clinicians in assessing the effectiveness of nutritional practices at their respective neonatal units.

As discussed in Chapter 1 (1.4.3), factors such as clinical traditions, availability of milk feeds, and resource limitations in hospitals may influence the adoption of different feeding practices in neonatal units around the world (276). This is evident

from previous studies that have showed variation in nutritional practices in feeding interventions in the neonatal units between countries, or even within the same country due to the adoption of different feeding protocols (267,277).

Several studies have compared nutritional practices between different neonatal units both within the UK and also with other countries. These studies have been mostly performed through surveys and retrospective review of medical records (4,11,1). Many of these studies have shown that how postnatal growth failure still consistently occurs, regardless of the updated and contemporary recommendations on nutritional practices being suggested and implemented (277,280). This might be due to problems translating evidence into practice or to inconsistencies in implementation itself, which has been shown to vary in different neonatal units (281).

There is a paucity of studies in this area of preterm infants feeding among South East Asian (SEA) infants, especially in Malaysia. A study on nutritional practices and growth outcomes from a neonatal unit in Malaysia was last performed in 2011 (250). This study was over a decade ago and not much research has explored the impact of improvements in neonatal care or considered whether it is feasible to compare nutritional practices in upper-middle income settings with a higher income country setting. Therefore, this current study will present an updated observational data to demonstrate the provision of nutritional care and growth assessments in the neonatal unit in Malaysia and provide a comparison with that to a higher-income country such as the UK.

This prospective observational study aims to evaluate and compare nutritional practices in feeding preterm infants in neonatal units in Malaysia and the UK and assess the association between feeding practices and growth outcomes at

discharge. The knowledge gained may lead to suggestions for improvement in feeding practices in both the neonatal units studied and more generally.

## 2.2 STUDY OBJECTIVES

The objectives of this study are as follows:

1. to compare major feeding practices and nutritional intakes between preterm infants cared for in the UK with those in Malaysia
2. to compare the growth outcomes of preterm infants during admission and at discharge at the two study sites
3. to investigate the factors associated with growth outcomes at discharge at the two study sites

## 2.3 METHODOLOGY

### 2.3.1 Study design

This is a prospective observational study of preterm infants (gestational age (GA) <34 weeks) in the neonatal units in two university hospitals: Hospital Canselor Tuanku Muhriz (HCTM), Malaysia and Royal Derby Hospital (RDH), United Kingdom. This collaborative study was a detailed review of medical records of preterm infants < 34 weeks GA who were born, admitted and discharged from these neonatal units between May 2019 and March 2020.

### 2.3.2 Study setting

The UK neonatal unit is a Local Neonatal Unit (level II) (282) routinely caring for infants born at >25 weeks' gestation. It provides care for the stable to intensive care infants. Its neonatal intensive care unit is one of three level III units in the Trent Neonatal Network. There are 24 cots, with 7 intensive care/ high dependency

spaces and 15 special care spaces. The unit also provides rooming in facilities for babies with their parents for when they are ready for discharge home.

Based on the categories of care by British Association Of Perinatal Medicine (BAPM) (282), this unit provides intensive and high dependency care as detailed below:

• intensive care: for infants requiring any form of mechanical respiratory support via a tracheal tube, both non-invasive ventilation (e.g. nasal Continuous Positive Airway Pressure (CPAP), SIPAP, Bilevel Positive Airway Pressure (BIPAP), nasal high flow) and parenteral Nutrition (PN), day of surgery (including laser therapy for retinopathy of prematurity (ROP)) and on day of death or any conditions listed as per BAPM categories of care.

• high dependency care: for infants requiring any form of non-invasive respiratory support (e.g. nasal, CPAP, SIPAP (infant flow system with multiple modalities), BIPAP, nasal High Flow, PN or continuous treatment of their condition as per BAPM categories of care.

More immature infants and those requiring surgical care are transferred to appropriate centres, for example for cardiac surgery (Leicester) or neonatal surgery (Nottingham). In general, the Obstetric Unit of the hospital deals with over 5,000-6000 deliveries a year. The neonatal unit has approximately 400 admissions per year including 200-300 preterm infants.

The Malaysian neonatal unit is considered a tertiary neonatal unit (level IIIb) (283) based on the local policy which also provides surgical support on-site (except for cardiac surgery). This unit also routinely care for infants >25 weeks GA but may support infants of 23-24 weeks GA if necessary. The unit has 26 cots which include

8 intensive cots, 8 semi-intensive cots and 10 convalescent cots. For isolation in infective cases, there are 8 cots provided in the unit.

According to the definition by Malaysia Pediatric services Policy (283), this unit also provides both intensive and high dependency care which cover services and procedures as below ( and all lower levels procedures required):

• high dependency intensive care: for neonates requiring assisted ventilation, intra-arterial blood pressure monitoring, continuous cardiorespiratory monitoring, PN, central venous catheterisation, transcutaneous blood gas and oxygen saturation monitoring and neonates requiring stabilisation following major surgery.

• low dependency intensive Care: for neonates requiring CPAP, continuous cardiorespiratory monitoring, intraarterial blood pressure monitoring, PN, central venous catheterisation, oxygen therapy in excess of 40%, and acute surgical nursing.

In general, the hospital caters for about 6000 births per year, and total admissions to the neonatal unit is about 480 per year, with 75-80% of them are preterm infants (about 360 admissions per year).

Therefore, between these two study units, although they are categorised differently due to the difference in the classification in the categories of neonatal care between UK and Malaysia, the level of care is similar aside from the absence of inhouse surgical support in the UK unit but both centres care for similar numbers of the target population i.e. <34 week infants. The Malaysian unit cares for surgical infants but these are usually in the majority term born infants with congenital malformations who are not included in this study. Both units have similar range of preterm infants admission per year and number of beds and both provide all three similar levels of medical care (stable, high dependency and intensive) to the range of infants in this

study. Both hospitals follow similar discharge criteria including weight of at least 1800g, not needing any additional medical support, and fully milk fed.

### 2.3.3 Ethical approval

Ethical approval was obtained from the HRA and Health and Care Research Wales (HCRW) Approval (United Kingdom) [IRAS project ID: 258817, Protocol number: 19012] and Research Ethics Committee, National University of Malaysia, UKM (Malaysia) [JEP-2019-325] (Appendix 2 and Appendix 3). No parental consent was sought as this is an observational study using routinely recorded clinical data.

### 2.3.4 Study participants

A total of 100 participants (50 from each site) who were admitted to the neonatal units were included in the study based on the inclusion and exclusion criteria below. Infants were recruited consecutively from May 2019 until the sample size of 50 was reached at each site.

#### 2.3.4.1 Inclusion criteria

- Preterm infants born at < 34 weeks' gestation (up to and including those born at 33 weeks + 6 days gestation)
- Born and admitted within 24 hours of birth to the participating neonatal units
- Not transferred out for any part of their neonatal care
- Length of stay of at least 14 days

#### 2.3.4.2 Exclusion criteria

- Infants with major congenital anomalies or malformations, genetic abnormalities, and critical illness with short life expectancy

- Missing more than 3 days of records of growth or nutritional intake that could not be retrieved, estimated or analysed
- Discharged or death at < 14 days

Infants with incomplete records were excluded to ensure there were adequate data for calculation of nutrient intake and to analyse growth outcomes at least by day 14 of life.

Preterm infants born < 34 weeks GA were chosen as main criterion as preterm infants born at 34 weeks or greater GA are not routinely admitted to the neonatal unit and if admitted, usually stay for less than 2 weeks (284).

Infants with short length of stay or critical illness with short life expectancy were excluded as they were unlikely to have had the opportunity to receive a sufficiently long period of adequate nutrition to demonstrate growth.

#### 2.3.4.3 Sample size

A formal sample size calculation was not performed for this study. The sample size was determined based on the usual admission numbers and length of stay at the neonatal units of both countries, with the aim of ensuring that daily data collection from birth to discharge was feasible within the time and resources available for the study. For both neonatal units, usual monthly admissions of preterm infants (< 37 weeks GA) range from 30 to 50 infants (annual admission of 360 to 600 infants). Therefore, collection of data from 50 infants from each unit was deemed to be achievable.

### 2.3.5 Data collection procedures

The data collection began after Ethics and Research and Development approvals from the respective neonatal units were obtained. Eligible infants were identified from the admission records. In the UK unit, HAH accessed all the data from the admission book, nursing charts and paper medical records, while two research nurses (JA and CS) with access to the electronic medical record system used in the UK unit called as BadgerNet (Client version 2.9.1.0) filled in the detailed morbidity data and any missing demographic information from the system. In Malaysia, a research assistant (TTL) retrieved all data electronically in HCTM using the Total Hospital Information System (THIS) called Caring Hospital Enterprise System (C-HEtS) as well as the paper medical records.

HAH designed and created a bespoke data collection form using Microsoft Excel (Version 16.43, Microsoft Corporation, 2018)(285) (Appendix 6) that was used at both centres to collect data from the source documents. Frequent communications via email and Skype meetings were used throughout the study period between HAH and TTL to ensure a consistent process of data collection from inclusion of participants to types and details of data collected. Monthly data quality checks for Malaysian unit's data were performed by monthly submission to HAH. Ongoing queries were raised and resolved accordingly.

The following steps were taken to extract relevant data for each eligible infant:

- any preterm infants born < 34 weeks GA were first listed in the study admission sheet. Admission and basic demographic information were collected from the unit admission book and each infant was given a unique, anonymous study number.
- paper medical records and nursing charts were reviewed each weekday to extract daily/weekly anthropometric information, nutrition/feeding data and

information on the infant's clinical condition. If an infant was discharged on a Saturday or Sunday, their final day(s) of records were retrieved from the unit's medical record office or hospital's main medical record department for review by the investigator.

- any missing information was retrieved electronically where possible and data entry from paper medical records or nursing charts were also double-checked continuously throughout the study period against original records by research nurses.
- any infants who were initially included in the study were later excluded if any of the exclusion criteria were met by their discharge day or earlier, such as those that stayed in the neonatal unit for fewer than 14 days.

### 2.3.6 Data items collected

Baseline demographic data were collected on study entry. Daily data were collected from the day of birth until the day of discharge. Data on clinical outcomes were recorded at discharge.

**Baseline and demographic data:** GA at birth; mode of delivery; mother's age; parity; Apgar score at 5 minutes; method(s) of resuscitation required (stimulation only/positive pressure stimulation/chest compression/drugs); and mother's antenatal steroid use. In the Malaysian unit, GA is determined by using early first trimester ultrasound or by estimation based on last menstrual period for those who presented in later pregnancy. In the UK unit, GA was determined by early first trimester ultrasound. These records were retrieved from both paper and electronic medical records.

**Daily feeding data**: volume of glucose; PN (starter and total PN solutions); volume of lipids; other fluids (not including medications and blood products); volume of enteral

feeding from expressed breast milk; fortified breast milk; or infant formula; and other supplements (e.g. Myotein).

**Clinical outcome data**:

- late onset sepsis (LOS): culture proven sepsis after 72 h of birth
- necrotising enterocolitis (NEC): based on clinical or radiological features that needed at least 5 days of withheld feeding and antibiotics
- intraventricular Haemorrhage (IVH): diagnosis of IVH of Grade 1 to 4
- periventricular leukomalacia (PVL): diagnosis of cystic PVL demonstrated on cranial scan
- chronic lung disease (CLD): requiring respiratory support including any supplemental oxygen at 36 weeks PMA
- retinopathy of prematurity (ROP): any stage diagnosed on screening examination
- patent ductus arteriosus (PDA): any diagnosis of PDA recorded (diagnosed on echocardiography).

All diagnoses were noted from clinical records (paper or electronic) and were recorded on the conditions as either Yes (had a diagnosis) or No (no diagnosis).

**Growth measures**

Following recommendations on reporting growth-related outcomes in preterm infants by using the Standardised Reporting of Neonatal Nutrition and Growth outcomes (StRoNNG) checklist (146), growth data were reported from birth, using the Fenton 2013 growth chart as the growth reference. Weight, length and head circumference (HC) were recorded at birth and were updated in the charts weekly (only for weight and HC) until discharge in their unit of measurement (kg and cm). Length measurements at discharge were only available in the Malaysian unit as it

was not routinely collected in the UK unit. Missing measurements were replaced by the nearest to these points of birth or discharge date (within 3 days) or documented as unavailable if none were recorded within 3 days of discharge.

### 2.3.7 Generation of derived variables

The data collected were used to generate several derived variables, divided into 3 categories (Table 2.1).

**Table 2.1: Types of data generated from data collection**

| Nutrient intakes | Feeding practices | Anthropometric measures |
|---|---|---|
| Total energy, kcal/kg/d | Day of life (DOL) of initiation of parenteral and enteral nutrition | Days to regain birthweight |
| Total protein, g/kg/d | Days to reach minimum 120 ml/kg/d of enteral nutrition | Maximum weight loss from birthweight |
| Total fat, g/kg/d | Days to reach full enteral feedings | Birthweight Z-score |
| Total carbohydrate, g/kg/d | Duration of parenteral nutrition | Weight-for-age Z-score (at discharge) |
| Protein energy ratio (PER), g/100kcal/d | Day of life fortifier was started | Head circumference-for-age Z-score (at birth and at discharge) |
| Total fluids, ml/kg/d | Proportion of calories from PN, breast milk (with or without fortifier), formula milk, glucose solution from birth to discharge | Length-for-age Z-score (at birth) |
| Cumulative energy deficits, kcal/kg | Rate of feeding advancement to full feed | Changes in weight-for-age Z-score from birth to discharge |
| Cumulative protein deficits, g/kg | Types of milk received and breast milk received during admission, at discharge and exclusive breast milk at discharge | |
| Cumulative fat deficits, g/kg | | |
| Cumulative carbohydrate deficits, g/kg | | |
| Cumulative fluid deficits, ml/kg | | |

#### 2.3.7.1 Calculation of nutrient intakes

For calculating nutritional intakes, an infants' birth weight was used as the day's working weight until the recorded weight exceeded the birth weight. Thereafter, the daily weight was taken to be the last available recording of weight. Methods of calculation for each variable are described below:

- total daily fluid intake, ml/kg/d: sum of all fluid intake on the day (IV fluids, PN, and milk divided by the infant's working weight for the day
- daily total energy intake, kcal/kg/d: sum of all calorie intake from glucose (5%, 10%, 12.5%, 15% or 20%), PN (including Vaminolact ®), lipid, breast milk or fortified breast milk, formula milk, and other supplements such as Myotein® divided by the infant's working weight for the day
- daily protein intake, g/kg/d: sum of all protein intake from all protein sources (PN (including Vaminolact ®), breast milk or fortified breast milk, formula milk, and other supplements such as Myotein®) divided by the infant's working weight for the day
- total fat intake, g/kg/d: sum of all the lipid intake from all lipid sources (parenteral lipid, breast milk or fortified breast milk, formula milk, and other supplements such as Myotein®) divided by the infant's working weight for the day
- total carbohydrate intake, g/kg/d: sum of all the carbohydrate intake from all carbohydrate sources (PN (based on glucose %), breast milk or fortified breast milk, formula milk, and other supplements such as Myotein®) divided by the infant's working weight for the day
- protein energy ratio (PER), g/100kcal/d: divide the day's total protein intake by the total calorie intake and multiply by 100
- daily nutrient deficits: Deficits were calculated as the difference between the actual intake and the minimum intake recommended by the ESPGHAN

recommendation. This specifies a minimum of 110 kcal/kg/d for energy intake, 3.5g/kg/d for protein (infants with ≥1 kg birthweight), 4.0 g/kg/d protein (infants with <1 kg birthweight), 4.8 g/kg/d for fat, 11.6 g/kg/d for carbohydrate and 135 ml/kg/d for fluid.

- cumulative nutrient deficit: sum of the daily deficit adding up with the total deficits from a day (s) before.

For weekly intake data, to reduce variations due to different lengths of stay, weeks were determined individually for each infant by dividing the duration of stay into reasonably equal time periods where each week of stay equalled 7 days, but the final or discharge week could range from 4 to 10 days. Although this final week might have more or less than 7 days, average nutrient intakes were divided by the number of days, so that all data are presented as ‘g/kg/d or kcal/kg/d’ rather than a total per week. This was adapted from previous studies (39,286) and did not significantly affect the study analysis, since the majority of infants are usually transferred into a ‘flat’ for room-in with the mother in the final few days before discharge where direct breastfeeding was more frequent and nutrient intakes were usually approximated.

There was no record of volume of milk consumed via direct breastfeeding collected in this study. Both units do not practice a routine to record before and after feeding weight for the calculation of direct breast milk consumed. However, as most infants in this study had direct breastfeeding only a few days before discharge home which mostly accompanied by bottle-feeding, analysis of milk intakes were done in clusters (week 1-4 or week 5-8) to accommodate for the possible ‘missing’ volume of milk recorded for such cases.

Based on this rational, and to allow for infants’ different lengths of stay and the reduced number of infants due to discharge with each advancing week, total nutrient intakes were categorised into 2 groups:

i) average weekly intake from week 1 until week 4

ii) average weekly intake from week 5 until week 8.

This also ensured a comparable number of infants from each unit in each time period. There were 50 infants in each unit at weeks 1-4 and there were 28 and 23 infants at weeks 5 to 8 in Malaysia and the UK units respectively.

Table 2.2, Table 2.3, Table 2.4 show breast milk fortifier, formula milk and PN composition used at the participating units. The nutrient composition calculation for both intakes of EN and PN were based on the daily volume and different brands of formula milk, breast milk fortifier and PN regime used in each unit as indicated in the medical records. The composition of breast milk was based on the systematic review of preterm milk composition (82). Standard feeding protocols use by both units are available in Appendix 4 and Appendix 5, while sample proforma used for data collection and calculation of nutrients is available in Appendix 6.

**Table 2.2: Nutrient composition of breast milk (per 100 ml)**

| | **Breast milk** | **Breast milk** | **Fortified EBM with Nutriprem** | **Fortified EBM with Nutriprem BMF** | **Fortified EBM with Similac® BMF** | **Fortified EBM with Similac® BMF** |
|---|---|---|---|---|---|---|
| **Used in** | Both (week 1) | Both (week 2 onwards) | UK (week 1) | UK (week 2 onwards) | Malaysia (week 1) | Malaysia (week 2 onwards) |
| **Energy, kcal** | 57 | 66 | 73 | 82 | 71 | 80 |
| **Protein, g** | 1.9 | 1.27 | 3.1 | 2.47 | 2.9 | 2.27 |
| **Fat, g** | 2.59 | 3.46 | 2.59 | 3.46 | 3 | 3.86 |
| **CHO, g** | 6.55 | 7.34 | 9.4 | 10.1 | 8.4 | 9.1 |
| BMF, breast milk fortifier; EBM, expressed breast milk; CHO, carbohydrate | | | | | | |

Source*s:* Manufacturers' literature for Similac® Human milk fortifier powder, Abbott Laboratories, Ross Products Division, Columbus, OH; Cow & Gate Nutriprem human milk fortifier, Nutricia Ltd, White Horse Business Park, BA14 OXQ

**Table 2.3: Nutrient composition of formula milk (per 100 ml)**

| | Nutriprem 2 | Nutriprem 1 | Enfamil A.R. | Similac ® NeoSure ® | Similac ® Special Care® 24 | Myotein ® |
|---|---|---|---|---|---|---|
| **Used in** | UK | UK | Malaysia | Malaysia | Malaysia | Malaysia |
| **Energy, kcal** | 75 | 80 | 67 | 74 | 81 | 415 |
| **Protein, g** | 2 | 2.6 | 1.69 | 2.1 | 2.4 | 79.8 |
| **Fat, g** | 4 | 3.9 | 3.46 | 4.1 | 4.41 | 8 |
| **CHO, g** | 7.4 | 8.4 | 7.6 | 7.5 | 8.4 | 6.1 |

Sources*:* Manufacturers' literature for Similac® NeoSure® and Similac® Special Care® 24, Abbott Laboratories, Ross Products Division, Columbus, OH; Cow & Gate Nutriprem, Nutricia Ltd, White Horse Business Park, BA14 OXQ; Enfamil A.R., Mead Johnson Products Division, Evansville, IN; Myotein®, Valens Nutrition, Bedford Business Park, Off Jalan Klang Lama, 58000 Kuala Lumpur.

**Table 2.4: Nutrient composition of parenteral nutrition (per 100 ml)**

| | Vaminolact ® 6.5% | Intralipid® 20% or SMOFlipid ® 20% | Parenteral nutrition 10% | Parenteral nutrition 12.5% | Parenteral nutrition 15% |
|---|---|---|---|---|---|
| **Energy, kcal** | 24 | 200 | 60 | 74 | 88 |
| **Protein, g** | 6.5 | NA | 3 | 3.5 | 4 |
| **Fat, g** | NA | 20 | NA | NA | NA |
| **Carbohydrate, g** | NA | NA | 12 | 15 | 18 |

Sources*:* Manufacturers' literature for Vaminolact® , Intralipid ® 20% and SMOFlipid ® 20% , Fresenius Kabi

### 2.3.7.2 Determination of feeding practices

Data on feeding practices were analysed individually for each infant in each unit. Day of birth was assigned as day 1 of life irrespective of the time of birth. As all infants were admitted on their first day of life, the duration of time taken, or day of life recorded for feeding practices are the same. Below is the description of each variables:

- day of life of at initiation of parenteral nutrition (PN): day of life when PN was first started
- day of life at first enteral milk feed: the first day of enteral milk feed received, with or without PN

- day of life achieving a minimum 120 ml/kg/d of feeding: day of life reaching 120 ml/kg/d of feeding or to the nearest amount if no accurate amount recorded. This may include a combination of parenteral and enteral feeding or only either one.
- day of life to reach full enteral feeding: day of life when full enteral feeding (no PN) reached 150 ml/kg/d or to the nearest amount if no accurate amount recorded.
- duration of PN: the number of days infants received PN
- day of life when breast milk fortifier was started: day of life when first received breast milk fortifier
- proportion of calories from PN, breast milk (with or without fortifier), formula milk and glucose solution from birth to discharge: this was calculated by dividing the total calories from each source separately by the total calories from all sources and multiplying by 100 to give a percentage.
- for breast milk feeding: “primarily” breast milk intake is defined as where the volume of milk is greater or equal to 80% of total energy intake.

#### 2.3.7.3 Calculation of anthropometric variables

Z-scores, derived from the Fenton growth chart (287), were used for all three measurements (weight, head circumference, length) to control for variations in GA. The Research Bulk Calculator using completed weeks of GA available at http://www.ucalgary.ca/fenton/2013 (Appendix 7) was used to calculate the Z-scores for weekly weight and head circumference (HC) using PMA for each infant. SGA was defined as birth weight < $10^{th}$ centile for birth weight (5).

Days taken to regain birthweight were derived as the number of days taken for an infant to reach their birthweight after any initial postnatal weight loss in the first few

days of life. Where infants did not regain their birthweight before discharge, this was recorded as not applicable.

Maximum weight loss is calculated by subtracting daily weight from birthweight and analysing the percentage for each week.

Degree of postnatal growth was determined by subtracting the weight-for-age Z-score at birth from the weight-for-age Z-score at discharge. There are variations in the measurement of postnatal growth failure (PGF) for preterm infants among studies, with no agreed standard cut-off point of Z-score or growth percentile to define PGF as to date. Generally, growth failure is considered when there are declines in weight-for-age Z-score of >1.34, >1.28 or >2, but with different reference charts and postnatal periods used (288). In this study, we defined postnatal growth failure as a decrease in weight-for-age Z-score between birth and discharge of more than 1.28 (≥1.28) based on Fenton growth charts, using the number that represents the 10th centile in a distribution as used in previous studies (289,290). Detail discussion on the reasons why Fenton growth chart was used in the study is explained in Chapter 1: Growth assessment in 1.4.4.

### 2.3.8 Data analysis

All statistical analyses were performed using STATA 16.0 (Stata Corp. College Station, TX). Firstly, descriptive statistics were used to summarise the demographic and clinical characteristics of infants and their mothers. Data were presented using numbers and percentages for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median, range and inter-quartile range (IQR) for non-normally distributed continuous variables.

The characteristics of infants and mothers, feeding practices as well as growth outcomes in the UK and Malaysia cohorts were compared using the Student's t-test

or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate. Mean or median difference and 95% confidence intervals were calculated for nutritional intakes and growth outcomes value comparison between sites.

Given the large number of statistical comparisons here (multiple tests) and throughout this chapter, p-values are presented to 3 decimal places, and confidence intervals are given where appropriate, to enable the reader to judge the full weight of evidence.

Specific methods used to address the three study objectives are described below:

**Objective 1: To compare major feeding practices and nutritional intakes at the two study sites**

For this objective, enteral and parenteral feeding practices as well as week 1-4 and week 5-8 nutritional intakes and cumulative deficits were compared between the two study sites. P-values were determined by using the Student's t-test or Mann-Whitney U test for continuous variables, or by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

However, Student's t-test is chosen in presenting p-values in many variables when comparing between the two countries here due to the small sample size in this study as it is more able to detect differences between groups when the sample size is small, though it might not be possible to verify the assumption of normality. Mean/median differences with 95% CI were also calculated to give better view of the analyses. Line graphs showing the trend in mean intakes and deficits for each unit by postnatal week are shown for comparison.

**Objective 2: To compare the growth outcomes of preterm infants during admission and at discharge at the two study sites**

For this objective, growth outcomes at discharge as well as other variables collected at discharge, including peak weight loss, days to regain birthweight and length of hospital stay, were tabulated and compared between the two study sites. P-values were determined by using the Student's t-test or Mann-Whitney U test for continuous variables, or by Chi squared or Fisher's exact tests for categorical variables, as appropriate. Mean/median differences with 95% CI were also calculated. Next, line graphs showing the trend in mean weekly weight-for-age Z-score and head circumference-for-age Z-score for each unit are also shown for comparison.

**Objective 3: To investigate the factors that are associated with growth outcomes at discharge at the two study sites**

For this final objective, univariable linear regression was first performed separately for each study site to assess the unadjusted associations between demographic, clinical and feeding characteristics and the change in weight-for-age Z-score from birth to discharge. Given the small number of observations at each site (n=50) this was considered an exploratory analysis only and so we limited the number of explanatory variables whose association with the change in Z-score we assessed.

We excluded any variables with large amounts of missing data, including all feeding characteristics measured between weeks 5-8 as many babies were discharged before this point. We also excluded all clinical conditions where fewer than 10 babies experienced that outcome (the case for all clinical conditions assessed amongst UK infants and NEC, ROP and PVL in Malaysia). We also checked for correlation between variables and assessed the shape of the association with the

outcome and as a result excluded the categorical variables for GA, birthweight and small-for-gestational-age, retaining the continuous variables for GA and birthweight.

By using the backward stepwise regression method, variables which were statistically significant at the 5% significance level in the univariable analyses, and those deemed to be clinically important based on established knowledge, were entered into a multivariable model. The least statistically significant variables were discarded, one by one and the discarding stopped when each variable remaining in the equation is statistically significant. Likelihood ratio tests were used to build a final parsimonious multivariable model. Collinearity between variables was assessed using the variance inflation factor (VIF) with a VIF of less than 5 taken to indicate no substantial collinearity (291). Where variables were correlated, the variable most strongly associated with the outcome was retained.

For this objective, due to the multiple hypothesis testing, it is possible that Type 1 error, or specifically Family-wise Error Rate might still occur although we have limited the number of testing as explained above. In addition, attempts to correct this error through single or sequential methods were dispensed by the author as it may lead to false negatives (Type II errors) and a potentially significant outcome might be missed for an exploratory nature of this study.

## 2.4 RESULTS

In this section, the number of infants included in the study are presented in the flow chart (Figure 2.1). Next, the population baseline data are shown, which include infant and maternal characteristics at birth for the two study sites, followed by clinical characteristics of the study participants during admission until discharge. Main results are presented in turn according to the objectives that are stated earlier.

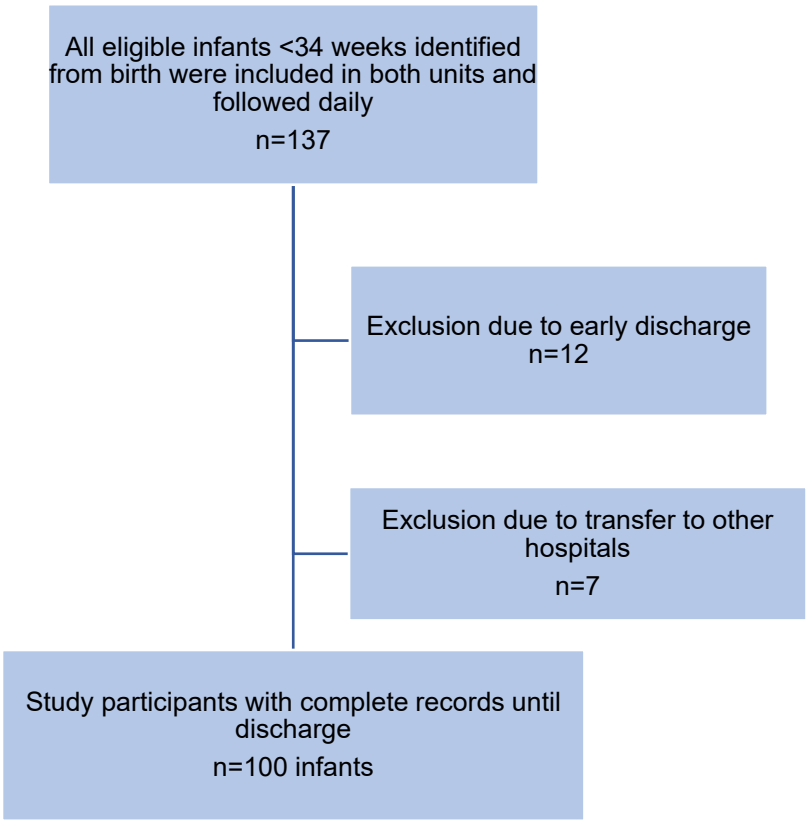



**Figure 2.1: Flow chart of infant recruitment**

Data collection ended when study participants with complete records reached 50 infants from each unit. There were 18 infants who have not been discharged yet (incomplete data) when the data collection has completed.

### 2.4.1 Characteristics of the study population

Table 2.5 shows baseline characteristics of the study participants including birthweight, GA, sex, and other at-birth anthropometric data. Between these two study sites, infants' sex and GA at birth measured on a continuous scale were comparable. However, for GA group, although the difference was not statistically significant, approximately half of infants in Malaysia were moderately preterm (54%) while the same percentage of infants in the UK were very preterm.

There were differences in birthweight and weight-for-age Z-score between infants in Malaysia and the UK. Mean (SD) birthweight among infants in Malaysia was lower at 1448 (458) g compared to 1649 (409) g in the UK infants, and mean (SD) weight-for-age Z-score was also lower in Malaysia than the UK (-0.53 (0.93) vs -0.10 (0.70)). There were more ELBW infants in Malaysia (20%) compared to the UK (6%). This helps explain the higher number of SGA infants (weight <10$^{th}$ percentile at birth) in Malaysia (24%) compared to only 6% SGA among UK infants (p=0.039).

Head circumference (HC) and HC-for-age Z-score were not appreciably different between units, but babies were born shorter and had a lower length-for-age Z-score at birth in Malaysia compared to the UK. Lastly, in the UK, there were more multiple births, mothers were younger and had had fewer previous births than in Malaysia.

**Table 2.5: Infant and maternal characteristics at the two study sites**

| Variables | Malaysia n=50 | UK n=50 | p-value |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 21 (42) | 22 (44) | 0.84 |
| Male | 29 (58) | 28 (56) | |
| **GA (weeks)**, median (IQR, range) | 32 (29-32, 25-33) | 31 (30-33, 26-33) | 0.736 |
| **GA group, n (%):** | | | |
| Moderate Preterm Infants (32-33 weeks) | 27 (54) | 21 (42) | 0.246 |
| Very Preterm Infants (28-31 weeks) | 19 (38) | 27 (54) | |
| Extremely Preterm Infants (<28 weeks) | 4 (8) | 2 (4) | |
| **Birthweight (g),** mean (SD) | 1448 (458) | 1649 (409) | 0.022 |
| **Birthweight-for-age Z-score**, mean (SD) | -0.53 (0.93) | -0.10 (0.70) | 0.009 |
| **Birthweight category, n (%):** | | | |
| Extreme low birthweight (<1000g) | 10 (20) | 3 (6) | 0.113 |
| Very low birthweight (<1500g) | 13 (26) | 16 (32) | |
| Low birthweight (<2500g) | 27 (54) | 31 (62) | |
| **Birthweight status, n (%):** | | | |
| Small for GA (<10$^{th}$ percentile) | 12 (24) | 3 (6) | 0.039 |
| Appropriate for GA (10$^{th}$-90$^{th}$) | 37 (74) | 45 (90) | |
| Large for GA (>90$^{th}$ percentile) | 1 (2) | 2 (4) | |
| **Head circumference (HC) at birth (cm),** mean (SD) | 28 (2.68) | 28.9 (2.35) | 0.106 |
| **HC-for-age Z-score at birth**, Median (IQR, range) | -0.26 (-0.98 to 0.59, -4.2 to 2.05) | 0.06 (-0.57 to 0.59, -3.3 to 1.54) | 0.310 |
| **Length at birth (cm),** mean (SD) | 38.4 (3.65) | 41.9 (4.08) | <0.001 |
| **Length at birth-for-age Z-score**, mean (SD) | -0.92 (1.05) | 0.21(1.23) | <0.001 |
| **Birth Status, n (%):** | | | |
| Singleton | 45 (90) | 34 (68) | 0.007 |
| Twin/triplets | 5 (10) | 16 (32) | |
| **Mother's age (years),** mean (SD) | 32 (5) | 29 (5) | 0.009 |
| **Parity**, median (IQR, range) | 3 (1-4, 1-8) | 0 (0-1, 0-6) | <0.001 |
| **Mode of delivery, n (%):** | | | |
| Caesarean section | 37 (74) | 32 (64) | 0.280 |
| Vaginal delivery | 13 (26) | 18 (36) | |

P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

Table 2.6 describes and compares the prevalence of various clinical conditions at birth and during admission until discharge for study participants at both study sites.

**Table 2.6: Clinical characteristics of infants from birth to discharge**

| Variables | Malaysia n=50 | UK n=50 | p-value |
|---|---|---|---|
| **Apgar score at 5 minutes,** median (IQR, range) | 9 (8-10, 3-10) | 9 (9-9, 6-10) | 0.844 |
| **Antenatal steroid use, n (%)** | 47 (94) | 42 (84) | 0.194 |
| **Resuscitation required, n (%):** | | | |
| None | 25 (50) | 13 (26) | 0.039 |
| Stimulation only | 4(8) | 7 (14) | |
| PEEP | 0 | 3 (6) | |
| Positive pressure ventilation | 21 (42) | 27 (54) | |
| **Late onset sepsis (confirmed), n (%)** | 13 (26) | 4(8) | <0.001 |
| **Necrotising enterocolitis (NEC, suspected), n (%)** | 6 (12) | 3 (6) | 0.243 |
| **Intraventricular haemorrhage (IVH), n (%)** | 36 (72) | 2 (4) | <0.001 |
| **Retinopathy of prematurity (ROP), n (%)** | 4 (8) | 1 (2) | 0.181 |
| **Periventricular leukomalacia (PVL), n (%)** | 7 (14) | 0 | 0.006 |
| **Chronic lung disease (CLD), n (%)** | 10 (20) | 3 (6) | 0.036 |
| **Patent ductus arteriosus (PDA), n (%)** | 16 (32) | 6 (12) | 0.014 |

P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate. PEEP; positive end-expiratory pressure

As Table 2.6 shows, there was no difference between sites in infants' Apgar score at 5 minutes after birth, nor in the proportion of mothers who received antenatal steroids. More infants in the UK cohort required any form of resuscitation (74% vs 50%). Infants in Malaysia had more morbidities diagnosed during admission for all the adverse outcomes tabulated, though for NEC and ROP the differences were not statistically significant at the conventional cut-off.

### 2.4.2 Objective 1: How do feeding practices and nutritional intakes compare between the two study sites?

For this objective, the frequency and types of milk received as well as the proportion of energy intake from different sources are compared between the two sites.

**Table 2.7: Feeding practices comparison between the two sites**

| Variables | Malaysia n=50 | UK n=50 | p-value |
|---|---|---|---|
| **Received any breast milk (own mother's) during admission, n (%)** | 49 (98) | 38 (76) | 0.001 |
| **Received any breast milk at discharge, n (%)** | 46 (92) | 25 (50) | <0.001 |
| **Exclusively breast milk feeding at discharge, n (%)** | 26 (52) | 16 (32) | 0.043 |
| **Received mixed feeding during admission, n (%)** | 39 (78) | 35 (70) | 0.362 |
| **Received infant formula milk, n (%)** | 40 (80) | 47 (94) | 0.037 |
| **Received human donor milk, n (%)** | 1 (2) | 0 | - |
| **Received intravenous fluids (IVF), n (%)** | 31 (62) | 21 (42) | 0.045 |
| **Received PN, n (%)** | 40 (80) | 19 (38) | <0.001 |
| **Energy proportion (%) from breast milk during admission, median (IQR, range)** | 66.5 (40-83,0-96) | 15.5 (2-82, 0-98) | 0.010 |
| **Energy proportion (%) from formula milk during admission, median (IQR, range)** | 19.2 (2.2-52.3, 0-95.7) | 78.8 (12.7-93.9, 0-99.7) | <0.001 |
| **Proportion (%) of energy intake from PN during admission, median (IQR, range)** | 6.0 (2.5-12.2, 0-47.5) | 0 (0-3, 0-28.5) | <0.001 |
| **Day of life at first parenteral nutrition, median (IQR, range)** | 2 (1-2,1-11) | 2 (1-2, 1-6) | 0.414 |
| **Day of life at first enteral milk feed, median (IQR, range)** | 2 (1-3,1-5) | 2 (1-2,1-4) | 0.833 |
| **Day of life reaching 120 ml/kg/d feed, median (IQR, range)** | 4 (4-5, 2-6) | 5 (4-5, 3-6) | 0.044 |
| **Day of life reaching full enteral feed at 150 ml/kg/d, median (IQR, range)** | 9 (7-12, 5-25) | 8 (7-10, 6-20) | 0.400 |
| **Rate of feeding advancement to full feed, ml/kg/d, median (IQR)** | 13 (6-16) | 16 (9-20) | 0.390 |
| **Duration of PN use, median (IQR, range)** | 9 (6-14, 3-36) | 6 (5-8, 3-12) | 0.031 |
| **Received breast milk fortifier, n (%)** | 43 (86) | 13 (26) | <0.001 |
| **Day of life at first breast milk fortifier received, median (IQR, range)** | 11(8-16,5-49) | 15 (10-20,8-45) | 0.039 |

P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

As Table 2.7 shows, more infants in Malaysia received their mother's own milk (98%) compared to infants in the UK (76%, p=0.001). More infants in the UK received infant formula milk (94%) compared to infants in Malaysia (80%, p=0.037). There were no differences in the proportion of infants in both units who received mixed feeding (breast milk and formula milk) during admission, p=0.362. More infants in Malaysia received PN during admission (80%) compared to infants in the UK (38%, p<0.001).

Infants in Malaysia had a higher percentage of energy intake from breast milk from birth until discharge, a median of 66.5% (40-83, 0-96), while infants in the UK had a higher percentage of energy intake from formula milk, with a median of 78.8% (12.7-93.9, 0-99.7). Consistently, at discharge, higher percentage of infants in the Malaysian unit received any breast milk feeding (92%, p<0.001) and exclusively breast milk feeding (52%, p=0.043) compared to UK infants.

Infants in Malaysia had a higher percentage of their energy intake from PN compared to infants in the UK, with a median of 6.0% (2.5-12.2, 0-47.5).

There were no differences between units in the day of life at the start of EN and PN, which occurred at median day 2 of life for both forms of nutrition. There was no difference between units with respect to the day of life at which infants reached full enteral feeding at 150 ml/kg/d, but there was a difference on day of life at which infants reached minimum feeding at 120 ml/kg/d (p=0.044).

Infants in Malaysia received PN for longer than infants in the UK (median 9 days vs 6 days, p=0.031). More infants in Malaysia received breast milk fortifier (BMF) than infants in the UK (86% vs 26%, p<0.001), and they also received it earlier than infants in the UK (day 11 of life vs day 15 of life, p=0.039).

Table 2.8 compares major nutrient intakes between study sites at week 1-4 and week 5-8, including energy, protein, protein energy ratio, fat, carbohydrates and fluid as well cumulative energy and protein deficits.

**Table 2.8: Infants' macronutrient intakes and cumulative nutrient deficits on weeks 1-4**

| | Week 1 to week 4 | | | |
|---|---|---|---|---|
| **Variables, mean (SD)** | **Malaysia n=50** | **UK n=50** | **MD (95% CI)** | **p-value** |
| **Energy intake, kcal/kg/d** | 103 (13) | 100 (11) | 2.87 (-1.92 to 7.65) | 0.238 |
| **Protein intake, g/kg/d** | 3.0 (0.5) | 2.7 (0.6) | 0.32 (0.10 to 0.54) | 0.004 |
| **Protein energy ratio, g/100kcal/d** | 2.82 (0.28) | 2.61 (0.48) | 0.21 (0.06 to 0.37) | 0.008 |
| **Cumulative energy deficit/excess±, kcal/kg** | -191.6 (129.8) | -254.5 (152.0) | 62.8 (6.79 to 118.98) | 0.028 |
| **Cumulative protein deficit/excess±, g/kg** | -11.4 (6.1) | -15.4 (8.0) | 4.05 (1.22 to 6.88) | 0.006 |
| **Fat intake, g/kg/d** | 4.8 (0.7) | 4.8 (0.6) | -0.06 (-0.32 to 0.20) | 0.627 |
| **Carbohydrate intake, g/kg/d** | 11.4 (1.9) | 10.7 (1.4) | 0.7 (0.13 to 1.44) | 0.020 |
| **Fluid intake, ml/kg/d** | 137.1 (12.9) | 138.8 (10.9) | -1.65 (-6.39 to 3.09) | 0.491 |

MD, Mean difference; 95% CI, 95% Confidence Interval, P-values for comparisons between the two groups were determined by the Student's t-test. ± Negative value indicates deficits

As Table 2.8 shows, both cohorts did not achieve the minimum recommended intake per ESPGHAN's recommendation for energy intakes of 110 kcal/kg/d in the first 4 weeks of life. There was a difference in total protein intake with infants in Malaysia receiving more protein than infants in the UK (3.0 vs 2.7g, p=0.004). Infants in neither Malaysia nor the UK achieved the minimum recommended protein intake based on ESPGHAN's recommendation of 3.5 g/kg/d.

There were also differences between units in the protein energy ratio (PER) with the PER being lower in infants in the UK compared to infants in Malaysia. Both units however failed to achieve the minimum requirement for PER based on ESPGHAN recommendation (3.2g/100 kcal/d).

There was a difference between units in cumulative energy deficit with infants in the UK had a higher negative deficit than infants in Malaysia with a MD of 62.8 kcal/kg (6.79-118.98). There were differences between units in cumulative protein deficit, with infants in the UK cohort having a higher negative cumulative deficit with the MD (95% CI) of 4.05 g/kg (1.22 to 6.88).

Finally, there were differences between units for carbohydrate intake (with intake being higher in Malaysia), but no differences in fat intake between units. These nutrient and fluid intakes in both units were above the minimum recommended intake by ESPGHAN (4.8 g/kg/d for fat, 11.6 g/kg/d for carbohydrate, 135 ml/kg/d for fluid), except for carbohydrate intake for infants in the UK which marginally lower than recommended.

**Table 2.9: Infants' macronutrient intakes and cumulative nutrient deficits on weeks 5-8**

| | Week 5 to week 8 | | | |
|---|---|---|---|---|
| **Variables, mean (SD)** | **Malaysia n=50** | **UK n=50** | **MD (95% CI)** | **p-value** |
| **Energy intake, kcal/kg/d** | 110 (18) | 115 (15) | -4.36 (-13.9 to 5.17) | 0.363 |
| **Protein intake, g/kg/d** | 3.4 (0.7) | 3.0 (0.8) | 0.37 (-0.06 to 0.79) | 0.088 |
| **Protein energy ratio, g/100kcal/d** | 3.03 (0.31) | 2.57 (0.38) | 0.45 (0.26 to 0.65) | <0.001 |
| **Cumulative energy deficit/excess±, kcal/kg** | 93.2 (237.4) | -93.8 (539.3) | 187.03 (-40.3 to 414.4) | 0.105 |
| **Cumulative protein deficit/excess±, g/kg** | -8.7 (11.8) | -24.5 (25.6) | 15.84 (4.96 to 26.71) | 0.005 |
| **Fat intake, g/kg/d** | 5.3 (1.0) | 5.8 (0.7) | -0.49 (-1.00 to 0.02) | 0.058 |
| **Carbohydrate intake, g/kg/d** | 11.9 (2.0) | 12.2 (1.7) | -0.27 (-1.33 to 0.79) | 0.607 |
| **Fluid intake, ml/kg/d** | 141.4 (22.4) | 153.9 (13.9) | -12.53 (-23.30 to -1.76) | 0.024 |

MD, Mean difference; 95% CI, 95% Confidence Interval, P-values for comparisons between the two groups were determined by the Student's t-test. ± Negative value indicates deficits

As Table 2.9 shows, both cohorts did achieve the minimum recommended intake per ESPGHAN's recommendation for energy intakes of 110 kcal/kg/d in the 5-8 weeks of life.

However, infants in neither Malaysia nor the UK achieved the minimum recommended protein intake based on ESPGHAN's recommendation of 3.5 g/kg/d.

There were differences between units in the protein energy ratio (PER) with the PER being lower in infants in the UK compared to infants in Malaysia. Both units however failed to achieve the minimum requirement for PER based on ESPGHAN recommendation (3.2g/100 kcal/d). There was an increase in PER in Malaysian infants at this period as compared to week 1-4, but a decrease in PER in the UK.

Both units seem to catch up at this point as there were decreases in energy deficits at both units since week 1-4, although the UK cohort still persisted with a negative deficit until week 8.

There were differences between units in cumulative protein deficits with infants in the UK cohort having a higher negative cumulative deficit with MD (95% CI) of 15.84 g/kg (4.96 to 26.71). Furthermore, the deficits in infants in Malaysian infants' intake improved at this point (although there were still deficits), but in the UK the magnitude of the deficits worsened.

Finally, there were differences between units for fluid intake (with intake higher in the UK). Fat, carbohydrate and fluid intakes in both units were above the minimum recommended intake by ESPGHAN (4.8 g/kg/d for fat, 11.6 g/kg/d for carbohydrate, 135 ml/kg/d for fluid).

Figure 2.2,Figure 2.3 and Figure 2.4 show trends in intakes for energy, protein, protein energy ratio as well as cumulative deficits for energy and protein from postnatal week 1 until postnatal week 8, comparing the two study sites.

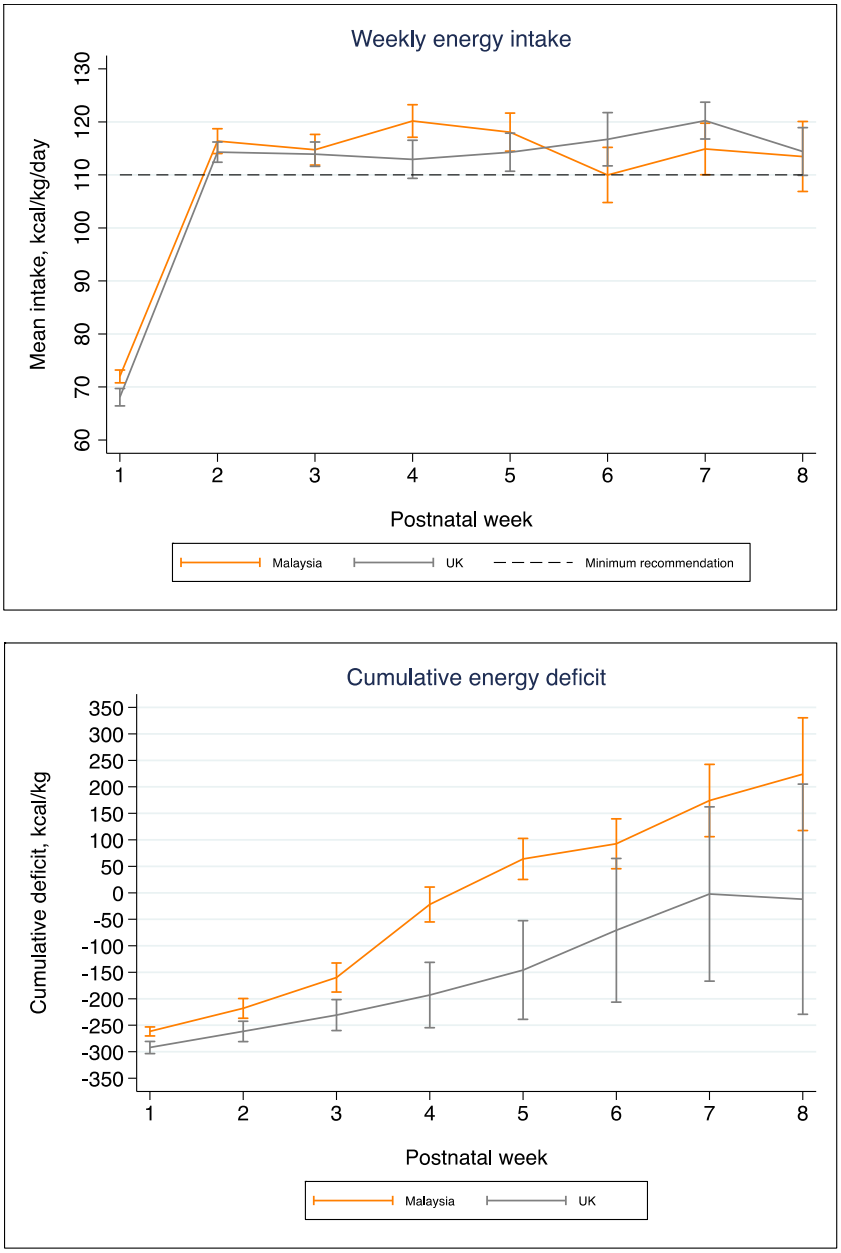



**Figure 2.2 : Mean weekly energy intake and cumulative energy deficits at the two study sites (error bars represent the standard error (SE))**

Figure 2.2 shows that energy intakes in both units were consistent at more than 100 kcal/kg/d after a sharp increase between week 1 and week 2 of life. However, cumulative deficit was negative in both countries from the first week of life. In Malaysia, energy intake increased and recovered to a surplus by week 5 of life. However, in the UK even though there was a consistent weekly improvement, the negative cumulative deficit persisted until week 8 of life.

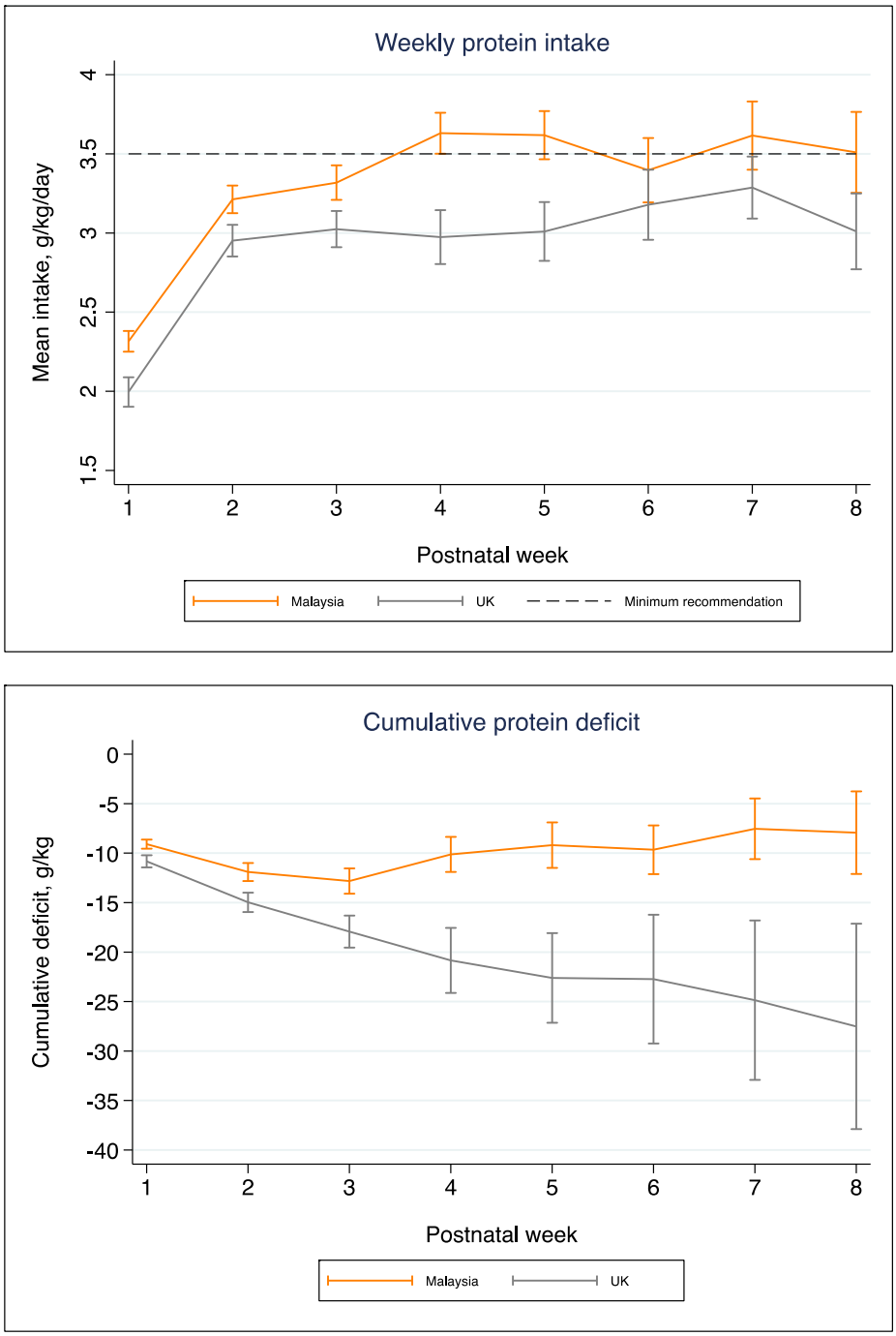



**Figure 2.3: Mean weekly protein intake and cumulative protein deficits at the two sites (error bars represent the standard error (SE))**

Figure 2.3 shows that infants in Malaysia had a higher protein intake throughout admission compared to infants in the UK and managed to reach the minimum recommendation of 3.5 g/kg/d by week 4-5 of life. Infants in the UK on the other hand had a slow increase in protein intake after week 2 of life but persisted with

lower than recommended protein intakes throughout until week 8, even though there was an increase in intake that occurred after week 5. For the cumulative protein deficit, these differences in trends in protein intake between the two units translates into the deficit graph where the mean deficit in Malaysia begins to slowly improve as early as week 3 of life and continues until week 8. However, for the UK unit, the deficit did not show any improvement and the mean negative deficit increased steadily until week 8.

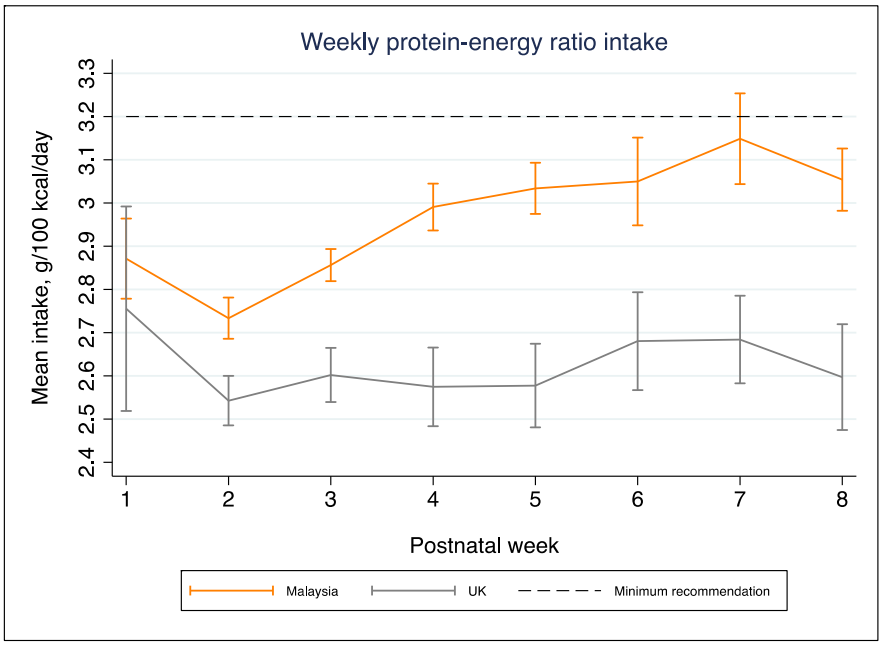



**Figure 2.4: Mean weekly protein-energy ratio intake at the two sites (error bars represent the standard error (SE))**

Finally, Figure 2.4 shows that infants in Malaysia had a higher mean protein energy ratio (PER) than infants in the UK throughout the first 8 weeks of life. There were also differences in trends between the two units. From week 2 of life, there was a sharp and consistent increase in PER for infants in Malaysia – this is consistent with the increasing protein and energy intakes shown in previous graphs, although it did not reach the recommended PER of 3.2g/100kcal/d. For infants in the UK, there was a slight increase in the PER after week 2 but generally it then remained steady until week 8.

### 2.4.3 Objective 2: How do growth outcomes of preterm infants at discharge compare between the two study sites?

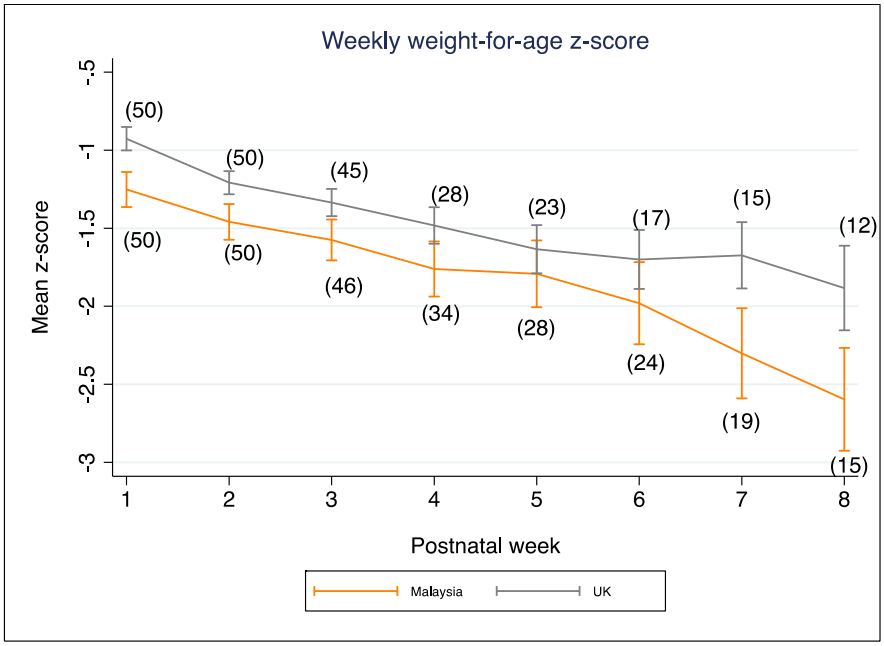
Postnatal growth outcomes at discharge, length of stay, as well as days to regain birth weight are summarised in Table 2.10 below and compared between the study sites.

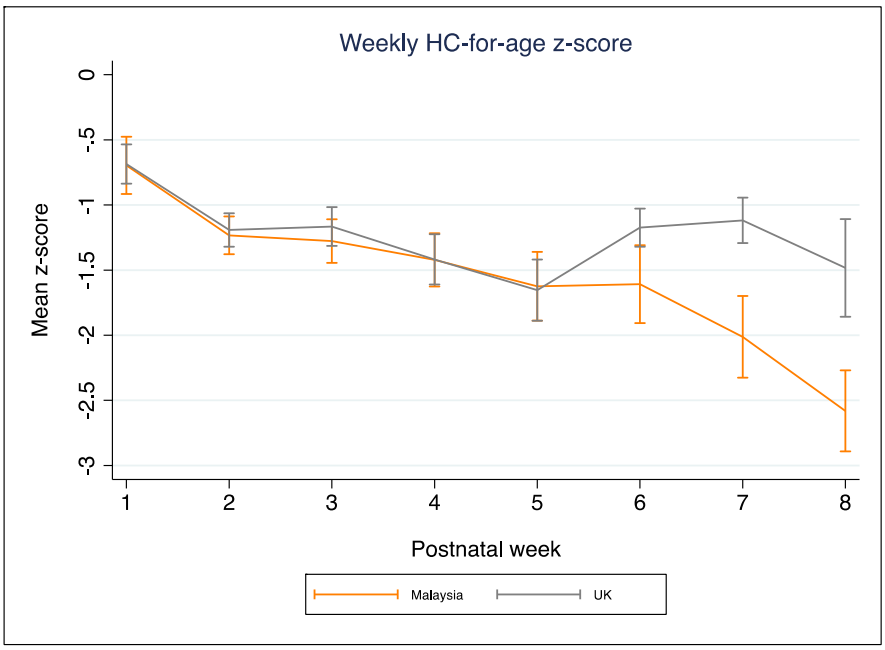
**Table 2.10 : Postnatal growth and other outcomes at discharge**

| Variables | Malaysia n=50 | UK n=50 | MD (95% CI) | p-value |
|---|---|---|---|---|
| **Days to regain birth weight, median (IQR, range)** | 12 (11-14, 6-19) | 13 (10-16, 6-27) | -1 (-3.17 to 1.17) | 0.247 |
| **Maximum weight loss from birth weight (%), median (IQR, range)** | 4.4 (1.9-7.5) | 5.7 (2.5-9.4) | -1.25 (-3.63 to 1.14) | 0.275 |
| **Weight (g) at discharge, median (IQR, range)** | 2060 (1890-2390, 1700-3480 | 2165 (2050-2380, 1700-2920) | -105 (-252.02 to 42.02) | 0.221 |
| **Weight Z-score at discharge, median (IQR, range)** | -1.65 (-2.32 to -1.0, -4.6 to 0.04) | -1.3 (-1.8 to -0.80, -3.6 to -0.3) | -0.35 (-0.77 to 0.08) | 0.088 |
| **Changes in weight Z-score from birth to discharge, mean (SD)** | -1.31 (0.57) | -1.33 (0.58) | 0.01 (-0.22 to 0.23) | 0.975 |
| **Infants with changes of weight Z- score of > - 1.28 from birth to discharge (postnatal growth failure), n (%)** | 26 (52) | 27 (54) | - | 0.841 |
| **Head circumference at discharge, (cm), mean (SD)** | 31.5 (1.61) | 31.4 (1.39) | 0.34 (-0.29 to 0.98) | 0.287 |
| **Head circumference Z-score at discharge, median (IQR, range)** | -1.33 (-1.69 to -0.59, -3.7 to 0.85) | -0.91 (-1.61 to -0.44, -3.64 to 0.34) | -0.42 (-0.87 to 0.04) | 0.383 |
| **PMA at discharge, median (IQR, range)** | 36.5 (35-38,33-42) | 36 (35-37, 34-41) | 0.50 (-0.53 to1.52) | 0.060 |
| **Length of stay (days), median (IQR, range)** | 36 (22-55, 14-112) | 28.5 (20-52, 14-74) | 7.5 (-3.87 to 18.87) | 0.157 |

MD, mean or median difference; 95% CI, 95% Confidence Interval, PMA, postmenstrual age
P-values for comparisons between the two groups were determined by the Student's t-test or Mann-Whitney U test for continuous variables and by Chi squared or Fisher's exact tests for categorical variables, as appropriate.

Table 2.10 shows that there were no differences between infants in Malaysia and the UK in days to regain birth weight, duration of hospital stay, PMA at discharge as well as all of the postnatal growth outcomes. More than 50% of the infants in both units were discharged home with postnatal growth failure (a change in weight-for-age Z-score from birth to discharge of > -1.28) and this also did not differ between units. The weekly measurements of weight-for-age Z-score (WAZ) and head circumference (HC) Z-score are shown in Figure 2.5.




Numbers in enclosed brackets indicate sample size at that time point for both measurements in the two neonatal units.

**Figure 2.5: Mean weekly weight-for-age z-score (WAZ) and head circumference (HC) Z-score (error bars represent the standard error (SE))**

Figure 2.5 shows that in both the UK and Malaysia unit there was a decreasing trend in mean WAZ from postnatal week 1 to week 8. Infants in the UK had consistently higher mean weekly WAZ than infants in Malaysia. There was a

decreasing trend in mean head circumference-for-age Z-score from postnatal week 1 to week 5 in both units. However, after week 5, the mean Z-score in infants in the UK increased before beginning to fall again in the final week, whereas infants in Malaysia continued to show a decreasing trend until week 8.

### 2.4.4 Objective 3: What factors are associated with growth outcomes at discharge and do these vary between the two study sites?

The descriptive data presented so far suggest that, on the whole, infants in Malaysia were sicker but received generally adequate nutrient intakes as per recommendations. On the other hand, infants in the UK were generally healthier, but did not receive adequate intakes as per recommendations. Despite these differences, in both cohorts mean weekly WAZ decreased over time and approximately 50% of infants had growth failure at discharge.

These observations lead to the exploratory analysis that follows to investigate factors that predict changes in WAZ from birth to discharge for infants at each unit. Table 2.11 below shows the unadjusted and adjusted associations between various demographic, clinical and feeding characteristics with the change in WAZ between birth and discharge.

As explained in the methodology section, univariable linear regression was first performed separately for each study site to assess the unadjusted associations between demographic, clinical and feeding characteristics and the change in weight-for-age Z-score from birth to discharge. Given the small number of observations at each site (n=50) this was considered an exploratory analysis only and so we limited the number of explanatory variables whose association with the change in Z-score we assessed. By using the backward stepwise regression method, variables which were statistically significant at the 5% significance level in

the univariable analyses, and those deemed to be clinically important based on established knowledge, were entered into a multivariable model. We excluded any variables with large amounts of missing data, including all feeding characteristics measured between weeks 5-8 as many babies were discharged before this point. We also excluded all clinical conditions where fewer than 10 babies experienced that outcome (the case for all clinical conditions assessed amongst UK infants and NEC, ROP and PVL in Malaysia). We also checked for correlation between variables and assessed the shape of the association with the outcome and as a result excluded the categorical variables for GA, birthweight and small-for-gestational-age, retaining the continuous variables for GA and birthweight.

**Table 2.11: Factors associated with the change in weight-for-age Z-score between birth and discharge**

| Variables | Malaysia | | UK | |
|---|---|---|---|---|
| | **Unadjusted β (95% CI), p-value** | **Adjusted β (95% CI), p-value** | **Unadjusted β (95% CI), p-value** | **Adjusted β (95% CI), p-value** |
| **Infant and maternal characteristics** | | | | |
| Female sex | 0.10 (-0.23 to 0.43), p=0.549 | | -0.02 (-0.36 to 0.32), p= 0.912 | |
| GA (weeks) | 0.14 (0.07 to 0.20), p<0.001 | | 0.05 (-0.05 to 0.15), p=0.316 | |
| Birthweight (g) | 0.001 (0.0003 to 0.001), p<0.001 | | -0.00002 (-0.0004 to 0.0004), p=0.890 | |
| Birthweight-for-age Z-score | 0.06 (-0.11 to 0.24), p= 0.482 | | -0.25 (-0.48 to -0.02), p=0.038 | -0.29 (-0.45 to -0.13), p=0.001 |
| Head circumference (HC) at birth (cm) | 0.10 (0.05 to 0.15), p= 0.001 | | 0.04(-0.03 to 0.11), p=0.222 | |
| HC-for-age Z-score at birth | 0.06 (-0.07 to 0.19), p=0.344 | | 0.01 (-0.15 to 0.17), p=0.893 | |
| Length at birth (cm) | 0.07 (0.03 to 0.11), p=0.001 | | 0.01 (-0.04 to 0.05), p=0.733 | |
| Length at birth-for-age Z-score | 0.04 (-0.12 to 0.19), p=0.642 | | -0.07 (-0.21 to 0.07), p=0.333 | |
| Multiple birth | -0.32 (-0.86 to 0.22), p=0.236 | | -0.25 (-0.60 to 0.11), p=0.164 | |
| Mother's age (years) | -0.02 (-0.05 to 0.01), p=0.159 | | -0.04 (-0.07 to -0.02), p=0.003 | -0.03 (-0.05 to -0.01) p=0.011 |
| Parity (firstborn/no previous completed pregnancy | - | | -0.15 (-0.49 to 0.18), p=0.365 | |
| Vaginal delivery | 0.11 (-0.26 to 0 .48), p=0.551 | | 0.07 (-0.28 to 0.41), p=0.702 | |
| Day regaining birthweight | -0.03 (-0.08 to 0.03), p=0.339 | | -0.07 (-0.11 to -0.04), p<0.001 | |
| Length of stay | -0.01(-0.02 to -0.01), p<0.001 | -0.01 (-0.02 to -0.01), p<0.001 | -0.01(-0.02 to 0.001), p=0.065 | -0.01 (-0.02 to -0.005), p=0.001 |
| **Clinical characteristics from birth until discharge** | | | | |
| Apgar score at 5 minutes | 0.08 (-0.02 to 0.19), p=0.109 | | -0.02 (-0.22 to 0.18), p=0.860 | |
| Antenatal steroid use | -0.29(-0.98 to 0.39), | | -0.27 (-0.72 to 0.18), | |

| | | | | |
|---|---|---|---|---|
| | p=0.393 | | p=0.235 | |
| Any resuscitation required | 0.05 (-0.28 to 0.39), p=0.744 | | -0.14 (-0.48 to 0.19), p=0.386 | |
| Late onset sepsis (LOS) | -0.17 (-0.54 to 0.20,) p=0.361 | | - | |
| Intraventricular haemorrhage (IVH) | -0.53 (-0.86 to -0.20), p=0.002 | | - | |
| Chronic lung disease (CLD) | -0.54 (-0.92 to -0.17), p=0.006 | | - | |
| Patent ductus arteriosus (PDA) | -0.25 (-0.59 to 0.09), p=0.152 | | - | |
| **Feeding Practices** | | | | |
| Received any breast milk | -0.31(-1.47 to 0.86), p=0.601 | | -0.30 (-0.68 to 0.08), p=0.124 | |
| Received infant formula milk | 0.18 (-0.22 to 0.59), p=0.370 | | 0.75 (0.08 to 1.42), p=0.028 | |
| Received intravenous fluids (IVF) | -0.47(-0.78 to -0.16), p=0.004 | | -0.37 (-0.69 to -0.05), p=0.023 | |
| Received parenteral nutrition | -0.40 (-0.79 to -0.01), p=0.047 | | -0.19 (-0.53 to 0.15), p=0.274 | |
| Energy proportion (%) from breast milk | -0.002 (-0.01 to 0.004), p=0.484 | | -0.01 (-0.01 to -0.003), p=0.001 | |
| Energy proportion (%) from formula milk | 0.003 (-0.002 to 0.01), p=0.265 | | 0.01 (0.003 to 0.01), p<0.001 | |
| Energy proportion (%) from PN | -0.01 (-0.03 to 0.01), p=0.243 | | -0.02 (-0.06 to 0.01), p=0.175 | |
| Day of life at first parenteral nutrition | 0.003 (-0.12 to 0.12), p=0.959 | | -0.14 (-0.45 to 0.17), p=0.342 | |
| Day of life at first enteral milk feed | -0.14 (-0.33 to 0.05), p=0.142 | | -0.01 (-0.22 to 0.20), p=0.916 | |
| Day of life reaching 120 mL/kg/d feed | -0.08 (-0.32 to 0.16), p=0.497 | | 0.02 (-0.19 to 0.22), p=0.879 | |
| Day of life reaching full enteral feed | -0.05 (-0.08 to -0.02), p=0.001 | | -0.08 (-0.14 to -0.02), p=0.013 | -0.05 (-0.09 to -0.004), p=0.030 |
| Duration of PN use | -0.04 (-0.07 to -0.01), p=0.004 | | 0.04 (-0.13 to 0.20), p=0.648 | |
| Received breast milk fortifier | -0.13 (-0.60 to 0.34), p=0.586 | | -0.31 (-0.68 to 0.06), p=0.101 | |
| Day of life first breast milk fortifier (BMF) received | -0.03 (-0.05 to -0.002), p=0.033 | | -0.03 (-0.06 to -0.0002), p=0.049 | |

| **Nutritional intakes in weeks 1-4** | | | | |
|---|---|---|---|---|
| Energy intake, kcal/kg/d | -0.006(-0.02 to 0.01), p=0.310 | | 0.02 (0.004 to 0.03), p=0.016 | |
| Protein intake, g/kg/d | -0.21(-0.51 to 0.10) p=0.178 | | 0.47 (0.20 to 0.74), p=0.001 | 0.36 (0.12 to 0.59), p=0.004 |
| Protein energy ratio, g/100kcal/d | -0.41(-0.98 to 0.16), p=0.158 | | 0.48 (0.15 to 0.80), p=0.005 | 0.34 (0.04 to 0.65), p=0.027 |
| Cumulative energy deficit, kcal/kg | -0.0001(-0.001 to 0.001), p=0.913 | | 0.002 (0.001 to 0.003), p=0.002 | |
| Cumulative protein deficit, g/kg | 0.015 (-0.01 to 0.04), p=0.246 | | 0.04 (0.02 to 0.06), p<0.001 | |
| Fat intake, g/kg/d | 0.05 (-0.18 to 0.28), p= 0.681 | | 0.36(0.10 to 0.62), p=0.008 | |
| Carbohydrate intake, g/kg/d | -0.07(-0.16 to 0.01), p=0.102 | | 0.07(-0.04 to 0.20), p=0.200 | |
| Fluid intake, ml/kg/d | -0.004(-0.02 to 0.01), p=0.542 | | 0.002(-0.01to 0.02), p=0.766 | |

Outcomes with <10 cases were not analysed and are marked as (-). CI, Confidence Interval. Adjusted β values are displayed only for variables that are included in the final model of regression.

In the Malaysian unit, infants, maternal and clinical characteristics showed that GA at birth, being very or extremely preterm infants, birthweight, being very or extremely low birthweight, HC and length at birth, length of stay, diagnosis of IVH and CLD are associated with changes in WAZ from birth to discharge in univariable analyses. For feeding practices, the use of IV fluid, PN, duration of PN, as well as day of life reaching full feed and first BMF use are associated with changes in WAZ. For nutritional intakes, none of the variables are associated with changes in WAZ in the univariable analyses. In the final model of multivariable regression analysis for this cohort, length of hospital stay is the only predictor that remain statistically significant in predicting changes in WAZ from birth to discharge, showing a more negative changes in WAZ with longer hospital stay (adjusted β of -0.01, p<0.001, adjusted $R^2$ of 0.35).

In the UK unit, infant and maternal characteristics which are birthweight-for-age Z-score, mother's age, day of life regaining birthweight, and length of stay demonstrated statistically significant association with changes in WAZ from birth to discharge in univariable analyses. For feeding practices, the use of formula milk, IV fluid, energy (%) from breast milk and formula milk, as well as day of life reaching full feed and first BMF use are statistically significant in association with changes in WAZ. Next, for weekly nutrient intakes, all nutrient variables except for carbohydrate and fluid intakes on week 1-4 are statistically significantly associated with changes in WAZ in univariable analyses.

However, when checking for collinearity, there were quite strong correlations between all of the average week 1-4 intake variables. Based on the established literature on the effects on growth, only average protein and PER intake were the intakes variables chosen to be included in the multivariable model instead of average energy, average fat or average cumulative protein/energy deficits. These variables were however added back in the last step of the final model to confirm that none of them become significant when excluded.

Therefore, in the final regression model (adjusted values in Figure 2.11) has shown that birthweight Z-score, mother's age, duration of hospital stay, protein intakes week 1-4, protein-energy ratio week 1-4 and day of life reaching full enteral feeds remain statistically significant in association with changes in WAZ from birth to discharge (adjusted $R^2$ of 0.62). Of these variables, protein intakes and protein-energy ratio (PER) week 1-4 gave positive coefficient indicating improved changes in WAZ with higher intakes of protein and PER at week 1-4, while higher birthweight Z-score, older mothers, longer hospital stay and more days taken to reach full feeds associate with more negative changes in WAZ.

## 2.5 DISCUSSION

The results show that half of the infants in this study cohort had postnatal growth failure at discharge, regardless of the study unit. There were significant differences in feeding practices and nutritional intakes of infants between the units, especially in the first 4 weeks of life, which should theoretically result in a more favourable growth outcome for some infants. However, non-nutritional factors such as infants' anthropometric measures at birth, clinical conditions during the hospital stay as well as maternal characteristics possibly exert a bigger influence on the growth outcome of these preterm infants at discharge.

### 2.5.1 Feeding practices in the two neonatal units

**More infants were fed with breast milk and there was a higher use of breast milk fortifier in the Malaysian unit**

For feeding practices, the term 'breastfeeding' that is discussed in this section is defined as any administration of breast milk (mother's own milk) or donor breast milk by any method of enteral feeding i.e. direct breastfeeding, or alternatives, such as cup, bottle or syringe. For the record, only one infant in this study (Malaysian unit) was recorded to receive donor breast milk for one week during admission.

There were significantly more infants in the Malaysian unit who received any intake of breast milk during the hospital stay as compared to infants in the UK unit. This is consistent with the national report by The National Health and Morbidity Survey (NHMS) (251) that recorded a high rate of breastfeeding (ever breastfed) among infants in Malaysia of 98% in 2016.

Similarly, in the UK, data from the Infant Feeding Survey 2010 (292) showed that 81% of mothers initiated breastfeeding, with recent data in England alone showing

the rate of breastfeeding initiation for 2016/17 of 75% (293). Both reports however are general for the whole nation's population and include infants of all gestations. Currently, there is no available data on national trends for both countries or international, on the prevalence of breastfeeding during admission in the whole preterm infant population in the neonatal unit or at discharge. However, a retrospective cohort study of the use of DBM in a neonatal unit in Scotland has shown that 60% of infants born < 32 weeks GA received MOM as first feed, and the majority (69%) of the recipient of DBM in the unit were born at <32 weeks GA, signifying the frequent use of breast milk in the unit for preterm infants and wide acceptance of DBM among these infants when MOM is not available (294). A large population study involving eight European regions found that the prevalence of breastfeeding among preterm infants was comparable with overall national breastfeeding rates in all infants (113), signifying similar breastfeeding practices and trends in the respective hospitals or countries.

However, at discharge, the percentages of infants who were still receiving any breast milk in this study decreased to only 50% in the UK unit, lower than the rate reported by the National Neonatal Audit Programme (NNAP) 2019 (253) at 60% of the same GA group, while 92% of infants in Malaysian unit in this study were receiving any breast milk or exclusively breastfeeding at discharge.

This reduction of breastfeeding practices at discharge has been reported in many studies with significant variation of rates between countries and even between neonatal units of the same country. Preterm infants were also shown to have not been breastfed for a longer duration and as extensively as term infants even when there was a high rate of breastfeeding initiation in the first few days or weeks after birth (295,295,296).

Among factors that might contribute to the high prevalence of breast milk feeding in the neonatal units are older maternal age (297), maternal higher education level (298), mothers from minority ethnic groups (253), primiparous (134), early enteral feeding ( <24 hours after birth), and received mother's own milk at first enteral feed (299). Additionally, breastfeeding support that consists of neonatal unit's environment and policy, nurses' roles and staffing adequacy, accreditation of a Baby-Friendly Hospital Initiative, and having general cultural attitudes to pro-breastfeeding highly contributed to the success rate of breastfeeding in the neonatal unit (122,298,299).

On the other hand, several hurdles associated with the failure or discontinuation of breastfeeding include pain during feeding or expression, maternal stress, perceived lack of milk adequacy, lack of support from healthcare professionals as well as infants' characteristics such as lower GA, multiple births, fetal growth restriction, severe neonatal morbidities, congenital anomalies and long hospital stay (295,298,300,301).

In this study, factors contributing to the higher rate of breastfeeding among Malaysian infants were possibly related to older maternal age and a higher number of mothers with previous pregnancies in the cohort. This is relevant as older mothers and especially ones with experience of previous children could theoretically have an easier start to breastfeeding or expressing breast milk, which could help in the initiation as well as the continuation of breastfeeding in the unit and after discharge home. In addition, the culture of breastfeeding within the Malaysian society is known to be very common as compared to the UK and the prevalence is increasing (302), and this might highly affect the breastfeeding rates among mothers in this study as well.

Furthermore, we know that GA reflects infants' maturity more accurately than birthweight (303). More than half of Malaysian infants who were moderately preterm, although with lower birthweight, may have been physiologically more mature and possibly could take breast milk more efficiently, at an earlier PMA and could sustain breastfeeding in the longer duration.

In terms of neonatal unit policy and staff support on breastfeeding in both units, both units have their feeding protocols that encourage breastfeeding based on the WHO recommendations such as breastfeeding initiation within an hour after birth and exclusive breastfeeding for the first 6 months of life (304). The minimum staffing standards for nurse: patient ratio for each category of neonatal care are also comparable between the units based on each country's guidelines which require neonatal intensive care to have 1:1 nursing for all babies, 2:1 nursing for all babies in high dependency care and 4:1 nursing for all babies in special care (23,282,283,305).

The only factor which could be the distinction between the two units' care environment in terms of breastfeeding support is the accreditation of Baby-Friendly Hospital which has been awarded to all government hospitals in the Malaysian unit since 1998 (254). The Baby-Friendly Hospital Initiative (BFHI) was launched by WHO and UNICEF in 1991 to encourage breastfeeding by improving breastfeeding initiation, duration, and exclusivity within hospitals and maternity units (306). Studies in many countries have shown that in Baby-Friendly accredited units, the numbers of infants receiving any breast milk are higher and the duration of any or exclusive breastfeeding, is longer (127,307,308), which what have been similarly indicated in the Malaysian unit. However, for the UK unit in this study, although full accreditation has not been received yet, Stage 1 accreditation was awarded in 2018 showing that policies and procedures to support the implementation of the BFHI standards have

been created and assessed to be adequate (309), though more aggressive approach could have been taken if full accreditation was granted.

In line with the higher use of breast milk in the Malaysian unit, significantly more infants also received breast milk fortifier (BMF) in the Malaysian unit as compared to the UK unit. In addition, BMF was given earlier in the Malaysian unit than in the UK. The variation in time when receiving the first BMF and for how long it was received in neonatal units have been shown in many studies possibly relating to inconsistencies in the guidelines used nationally and internationally (310). Some of the most common indicators for initiating BMF in the neonatal unit are birth at <32 or <34 weeks GA, birth weight of <1500 g (311,312) or <1800g (35) or faltering growth (313), weight gain <15 g/kg/d and enteral feeding at 150 ml/kg/d (310). Some units only add BMF when the infant 'needed it' as per healthcare professionals' advice, usually because of poor weight gain or low urea values (314).

For the units involved in this study, the standard protocol recommends the addition of BMF when the feeding reaches 75 ml/kg/d-100ml/kg/d in the Malaysian unit in which generally, the Malaysian unit still fortifies if breast milk is at least 50% of the total intake. The UK unit's protocol suggests for the addition of BMF when the feeding reaches 150-180 ml/kg/d, both for infants born <1500g or <32 weeks GA, but only at the clinician's discretion when there are significant concerns about growth. While there are no previous local studies found to compare Malaysia's data, previous survey studies showed an increase in routine BMF use in the UK's neonatal units from 2012 to 2020 with most neonatal units having guidelines on the use of BMF (310,314). The use of BMF in the UK is also known to be similar between different levels of care (315), although there were widely held beliefs regarding the use of BMF demonstrated among health care professionals.

On another view, this study also showed differences in usual practice on breast milk feeding between the units as the majority of infants who received breast milk in the Malaysian unit received BMF, while the majority of infants who received breast milk in the UK unit received supplemental formula feeding, as opposed to BMF. Interestingly, even when they received BMF, the majority of infants in the Malaysian unit were also receiving a certain amount of formula milk, while in the UK, BMF is less used when breast milk feeding is already supplemented with formula milk.

**More infants received PN and had a longer duration of PN in the Malaysian unit**

In this study, higher percentages of infants in Malaysia also received PN and received it for a longer duration than UK infants. Firstly, this might be due to the higher number of infants of extremely low birth weight and SGA which would qualify them for PN. Secondly, there were also more infants with co-morbidities in the Malaysian unit, which leads to infants being started on PN, for concerns on initiation of early enteral feeding. Although they were given some enteral feeds, they were also started on PN possibly due to anticipation of feed intolerance and slower advancement of milk feeds. PN was used in this scenario possibly, with a view to boost nutrition while milk feeds were established. Infants in the UK unit were larger and less unwell and hence more likely to establish enteral feeding quicker and hence PN use was restricted.

In addition, in the Malaysian unit, 60% of infants who received PN were VLBW and ELBW, median GA of 31 weeks, with mean birthweight of 1314g. This is consistent with the national guidelines indicated in the Malaysian unit's protocol to start PN for infants with birthweight <1000g or 1000-1500 (expected to have delayed significant feeds for ≥3 days) and >1500 (anticipated for delayed significant feed for ≥5 days) (316).

In the UK, various guidelines for PN initiation indicated the criteria as follow: GA at birth <30-31 weeks, or >30-31 weeks GA (with inadequate EN for >3-5 days) or birthweight <1250 g, while local protocol indicated routine PN for <30 weeks GA or ELBW (<1000g)(317,318). Consistently, post-hoc analysis showed that approximately 70% of infants who received PN in the UK unit were born ≤30 weeks GA, with a mean birth weight of 1235g, showing compliance as per the protocol.

Additionally, the post-hoc analysis showed that 93% of infants who received PN in the Malaysian unit also had at least one of these conditions: NEC (suspected), LOS, IVH, PDA, PVL, CLD, indicating sick/unstable infants while only half of the infants in the UK unit who received PN had any of the conditions mentioned. Therefore, in this study, the higher prevalence of PN use in the Malaysian unit was possibly due to a higher number of lower birthweight infants and SGA infants and more common co-morbidities recorded in the Malaysia unit.

This difference in PN use between units also expectedly did affect the overall nutritional intakes of infants especially in the 4 weeks of life which will be discussed below.

### 2.5.2 Nutritional intakes in the two neonatal units

#### Energy intakes and cumulative energy deficits

In this study, both units had comparable average energy intakes since week 1 of life and achieved a minimum recommended intake of 110kcal/kg/d on day 8-9 of life (week 1-2 of life). However, based on the overall weekly intakes, the Malaysian unit consistently had higher intakes in the first 4 weeks of life, before decreasing after week 5. On the other hand, UK infants had a persistent increase in energy intakes from week 1 until week 8. This different pattern of intakes possibly occurs since the

majority of infants in the Malaysian unit were still breastfeeding at week 4 or 5 of life ( at median PMA of 36 weeks) and some of them might have already had established direct breastfeeding routine in which the amount of milk that was recorded in the system are only the smaller amount supplemented by bottle feeding.

In terms of cumulative energy deficits, Malaysian infants seem to be able to overcome the deficits earlier at week 4 of life, while UK infants were constantly in negative deficits and almost recovering by week 7-8. This possibly occurred due to the persistent higher amount of energy intakes in the Malaysian unit, as a result of a higher number of infants with PN, longer duration of PN, as well as the common practice of BMF supplementation, even in addition to the mixed feeding of formula milk as shown in other studies (41). This has possibly helped to avoid high negative deficits from the early days of life which cumulatively would become more negative when infants gained weight and required more intake as recommended.

On the other hand, in the UK unit, although formula milk feeding was predominantly the main source of energy intake, which was seen to be helpful in slowly recovering the deficits, the progress to achieve positive deficits might take longer due to higher baseline deficits due to less than recommended intakes in the early weeks of life.

In terms of energy intakes, 98% of Malaysian infants had received any amount of breast milk in the unit, of which approximately 80% of them received a combination of fortified breast milk and formula milk. The majority of calories received were recorded from fortified breast milk. As for the UK unit, among 76% of infants who received any amount of breast milk, approximately 60% of them received a combination of unfortified breast milk and formula milk during admission. Formula milk contributed about 60% of the calorie intake. This could indicate the differences in the energy and protein intakes between the units as well as its effects on

recouping the deficits before discharge based on the nutritional contents of formula milk and fortified breast milk use.

**Protein intakes and cumulative protein deficits**

In parallel to energy intakes, Malaysian infants also persistently had higher protein intakes throughout admission than the UK infants and achieved the recommended protein intakes of 3.5g/kg/d earlier on week 3-4 of life. This is again, possibly largely contributed by the high prevalence of PN use among Malaysian infants as the increase in protein intake could be seen as slower after week 2 of life, when most infants had stopped PN and full enteral feeding has just been established. Additional amino acid solutions (Vaminolact; Fresenius Kabi) also were given to 30% of infants in the Malaysian unit to achieve a higher amino acid supply. In the UK unit, other than lower use of PN due to its more clinically stable, higher GA and higher birthweight infants in the cohort, the duration of PN was also shorter, although days reaching full enteral feeding did not differ between the units. This may explain the lower protein intakes recorded in this cohort.

As for enteral feeding, different sources of milk would also possibly contribute to the amount of protein intake. For example, post-hoc analysis of protein intakes showed that on week 3, when the majority of infants were already on full enteral feeding, infants in the Malaysian unit had a median of 3.3g/kg/d protein from a mix of fortified breast milk and formula milk (predominant feeding), 3.6g/kg/d protein from fortified breast milk only, followed by 3.0 g/kg/d from a mix of unfortified breast milk and formula milk. As for the UK unit, those on a mix of unfortified breast milk and formula milk (predominant) were recorded to have a median protein intake of 2.8 g/kg/d, 3.3g/kg/d from formula milk only, 3.5g/kg/d from a mix of fortified breast milk and formula milk.

This detailed analysis shows that when feeding was predominantly breast milk as observed in the Malaysian unit, fully fortified breast milk could provide more protein than a combination of fortified breast milk and formula milk. On the contrary, when feeding is predominantly formula milk as seen in the UK unit, supplementation of fortified breast milk would offer higher protein as compared to formula milk only, or mixed feeds of unfortified breast milk and formula milk.

Looking at the cumulative protein deficits, though both units had negative deficits from the first week of admission, the Malaysian unit quickly picked up and started to catch up after week 3 and continue to improve until able to slowly inverse the deficits in week 4 of life. Other than the use of routine BMF supplementation and formula feeding, the use of Myotein supplementation was also seen in approximately 46% of infants in the Malaysia unit. Even with this aggressive supplementation of protein, the deficits were not fully recovered until week 8 of life, or before most infants were discharged at week 5 (median hospital stay of 36 days). However, based on the interpolation of the graph, it could be recovered after 1-2 weeks post-discharge (around week 10), providing that these infants were discharged home with the same supplementation of protein that they received during admission.

However, for the UK infants, the cumulative deficits were worsening from the early days of life with no suggestion of recovery at/after discharge. This is probably due to the lack of compensation in a form of PN as seen in the Malaysian unit and inadequacy of enteral protein intake per recommendation value as discussed earlier. Since the minimum recommended protein intakes of 3.5 g/kg/d in the units were only adequate to account for the basic requirement for infants' growth, a higher target must be reached and should be started earlier if we were to catch up with the negative deficits, as seen in a previous study (24). Both cohorts also did not manage to achieve recommended PER at 3.2 g/100 kcal/d although Malaysian

infants had consistently higher PER and closely meet the recommendation after week 7.

In this study, in comparison to two earlier studies, Embleton et al. (24) and Senterre et al. (41) which used 120 kcal/kg/d energy and 3.0 g/kg/d protein recommendations as a reference value for ≤30 and ≥31 weeks GA infants (Embleton et al.) vs 120 kcal/kg/d and 3.8 g/kg/d reference value for ≤30 weeks GA (Senterre et al.), Malaysian cohort, in general, showed fewer cumulative protein deficits as compared to the infants of the similar GA group in Embleton et al.'s study but higher deficits as compared to infants of the same GA in Senterre' et al.'s study. This could be due to Senterre et al.'s study that has adapted 'optimised' nutritional protocol consisted of higher energy and protein intakes even since the first week of life. In Embleton et al.'s study, mean energy and protein intakes at week 1 were very low at 60kcal/kg/d and 1.0g/kg/d (1.0) (for ≤30 weeks GA infants) and 72 kcal/kg/d and 1.4g/kg/d (≥31 weeks GA infants).

On the other hand, mean energy and protein intakes during the first week of life for infants in Senterre et al.'s study were 79kcal/kg/d and 3.2g/kg/d (<28 weeks GA infants) and 79 kcal/kg/d and 3.1g/kg/d (28-30 weeks GA infants) respectively. Energy and protein deficits in Senterre et al.'s study recovered after week 6 of life, as compared to the Malaysian cohort where recovery is seen earlier after week 4 for energy deficits but predicted much later after week 10 for protein deficits.

However, similar to Senterre' et al.'s study (41), the use of a mixture of fortified breast milk and formula milk was also shown to provide ample amount of energy and protein intakes as demonstrated in the Malaysian cohort. On the other hand, Embleton's study supplemented unfortified breast milk with preterm formula (50: 50 ratio or 100% formula milk), which was similarly practised in the majority of infants in

the UK cohort of this study. It is possible that this difference in breast milk supplementation pattern led to the distinctive protein intakes between these studies.

Additionally, post-hoc analysis also showed that the UK units had a consistently higher average volume of enteral feeding given during the first 10 days of life with the rate of feeding increment before reaching full feeding being a median of 16 ml/kg/d as compared to 13 ml/kg/d in Malaysian unit. For example, on day 5, the median total fluid intake (including PN) in the UK unit was 122 ml/kg/d vs 140 ml/kg/d in the Malaysian unit. However, for enteral feeding only, the UK's median enteral feeding intake was higher at 85 ml/kg/d vs 40 ml/kg/d in the Malaysian unit, showing that predominant intakes in the Malaysian unit during early days were from PN and IV fluid.

However, comparing milk volume with nutrient density or its energy and protein contents on that particular day 5 for example, a higher number of intakes were seen in the Malaysian unit at 95 kcal/kg/d and 3.2 g/kg/d protein as opposed to 89 kcal/kg/d and 2.5 g/kg/d protein in the UK unit. This shows how much PN has contributed to the higher nutrient intakes among Malaysian infants in the early days of life, which possibly has contributed to minimising the cumulative energy and protein deficits. Nonetheless, any change to feeding strategies for the individual infant would also, understandably, be a response to infants' clinical conditions which might not be detected in this study.

Therefore, given the possibility of accumulated energy and protein deficits and the potential needs for catch-up growth in preterm infants, higher energy and protein requirements in a form of PN support (if required) and optimised nutritional intakes (i.e. use of BMF) should be aimed early to facilitate maximal protein accretion for these preterm infants and minimise nutritional deficits (37,41).

### 2.5.3 Postnatal growth at discharge in both neonatal units

Despite the differences in feeding practices – in terms of PN support and breast milk feeding with BMF supplementation, which contributed to the differences in weekly intakes and deficits, there were no differences between infants in Malaysia and the UK on days to regain birth weight, maximum weight loss as well as weight-for-age and HC-for-age Z-score at discharge. Throughout admission, the UK infants were observed to have consistently higher weekly weight Z-score than Malaysian infants, although both were persistently in the negative realm and decreasing trends. A similar growth pattern was observed for the weekly HC Z-score, though differences between units were much smaller. Infant in both units were discharged at approximately similar PMA of 36 weeks. Infants in the Malaysian unit stayed longer by approximately 7 days, though this difference was not statistically significant. More than half of the infants in both units were discharged home with postnatal growth failure defined as a change in WAZ from birth to discharge of ≥-1.28.

**Malaysian infants**

Among Malaysian infants, univariable analyses showed that infant characteristics had a greater influence in determining growth outcomes than nutrition intakes or feeding practices. Length of stay is the only variable that remained statistically significant in the final regression model, showing a lower WAZ with a longer hospital stay. This is possible due to the unit's common practice which pushes for faster weight gain for healthier or clinically stable infants for early discharge. This is practised due to the space limitation in the unit. Therefore, it is possible that infants who stayed for longer in the unit consists of non-clinically stable infants who could not afford to be fed more 'aggressively', hence had more cumulative nutrient deficits and poorer growth at discharge.

Previous studies also showed that hospital stay could be the predictor for growth failure at discharge due to the common situation in neonatal units where infants who had to stay longer were usually infants who had lower birthweight, SGA, younger GA, had clinical conditions or complications, had feeding problems or had slow growth (319,320). This is consistent with a local study that showed lower birth weight and extremely preterm infants stayed longer in the neonatal unit in Malaysia (321). Although few studies also showed that longer hospital stay could lead to better growth (i.e. greater weight gain) due to more careful monitoring and increase of nutritional intakes (256), the longer stay could also indicate that these infants are not ready to be discharged home early due to unsatisfactory growth or severity of medical conditions that need extra monitoring in the units as seen in previous studies (322).

However, length of stay was only accounted for approximately 35% of the variation in changes of WAZ from birth to discharge in the Malaysian unit and the small Beta coefficient of -0.01 also indicates a small effect size of this variable towards changes in WAZ, therefore, this needs to be interpreted with caution in clinical practice. There is possibility that other factors could also be contributing to WAZ changes but were not found to be statistically significant in this study. For example, baseline anthropometric assessment showed that there was a significantly higher proportion of SGA infants in the Malaysian unit. This couldbe due to the centre acting as a referral hospital for high-risk obstetric cases involving mothers with pre-eclampsia, diabetes and fetal growth restriction.

Infants in the Malaysian unit were also challenged with a higher incidence of co-morbidities such as CLD and PDA that likely necessitated the restriction of total fluid intake which could affect growth, as well as other clinical conditions such as late-onset sepsis (LOS) and IVH.  Although no direct association was found between

any of these clinical conditions and the growth outcome at discharge, possibly due to the small sample size, many studies have shown that sicker infants have poorer growth at discharge (256,323). This is possible as infants with more sickness are often fed differently, have increased metabolic requirements, needing higher nutritional intakes – which were rarely met, leading to a longer hospital stay as well as poor growth outcomes at discharge (273). Consistently, in this study, 60% of infants in the Malaysian unit who had any types of clinical conditions during hospital stay had growth failure at discharge. Although it is unknown if this was caused by the limited intake received or the inevitable effect of inflammation on nutrient accretion, studies presented that different types of illness or severity of the conditions might significantly affect nutritional status that eventually led to a greater accumulated nutritional deficit (269). This was also supported by the fact that more infants in this unit received PN, and also received it longer, as one of the common indicators of their “unwellness” as compared to the UK infants. However, the use of aggressive nutrition by the use of PN and optimised enteral intakes due to increased nutritional needs might have also prevented “being unwell” as the significant predictors to growth failure at discharge.

Additionally, although analyses showed better energy and protein intakes among Malaysian infants in this study than the UK infants, it was indeed a theoretical calculation based on the best available estimates (82) for the breast milk intakes. It is also known that breast milk composition between mothers varies greatly. In addition to the expression, storage, freezing process that happened in the unit, the Malaysian unit also practices routine pasteurisation for all expressed breast milk in the unit.

This standard pasteurisation process or Holder Pasteurisation which involves heating milk to 62.5°C for 30 minutes has been shown to be effective in eliminating viral and bacterial pathogens (324). A study in Malaysia found significant bacterial

contamination in the expressed breast milk (EBM) samples in Malaysian NICUs (325,326). However, studies have also shown that the practice of breast milk pasteurisation decreases the content of nutrients and bioactive compounds in breast milk (327). This includes components such as secretory IgA, lactoferrin, lysozyme, bile salt-dependent lipase and lipoprotein lipase as well as reduced macronutrient contents of lipids and protein, although in varying degrees. Although these factors and their bioactivity are reduced as compared to untreated breast milk, many beneficial compounds of human milk remain, even after pasteurisation. Pasteurised breast milk is, therefore, more beneficial than formula milk and has adequate nutrients to provide clinical benefits (324), though its impact on growth might be lesser than that of fresh expressed mothers milk given directly to the baby (328). Furthermore, any interpretation for 'optimal growth' outcome should explore factors other than weight only, including longer-term growth, neurodevelopmental, and metabolic outcomes in later life. Studies show that preterm infants fed mainly breast milk have better long-term outcomes despite slower weight gain in early life (67,329).

**UK infants**

Contrary to what has been analysed and discussed on Malaysian infants, univariable analyses showed minimal infants' characteristics factors but more nutrition-related factors to be associated with changes in WAZ at discharge. However, in the final model of regression, birthweight Z-score, mother's age, duration of hospital stay, protein intakes week 1-4, PER week 1-4 and day of life reaching full enteral feeds remained as the significant predictors for changes in WAZ at discharge that accounted for 62% of the variation.

Firstly, many studies have shown that LBW or low weight Z-score at birth or being SGA as one of the strongest negative predictors of weight gain or better growth at

discharge (256,330), possibly due to the fetal metabolic programming, that leads to efficient energy preservation in these smallest infants. On the contrary, in this study, infants with higher birthweight Z-score could negatively predict changes in WAZ growth at discharge. This could be due to how individual infants were managed in the unit when deciding on the nutritional intakes.

It's a common practice that when infants were born with good birthweight or birthweight Z-score and do not have any clinical condition that warrants closer attention, they would not commonly be put on an aggressive nutritional regime or closely monitored for intakes as these 'healthy' infants were expected to be thriving well. Furthermore, these infants were also normally got to be discharged early. This study also showed the same pattern as in the other studies that infants who were born 'normal' or appropriate-for-age (AGA) were eventually discharged home as having growth failure (255,286).

Interestingly, older maternal age was also the negative predictor for growth in this cohort. Advanced maternal age was shown in many studies to be associated with various maternal and perinatal morbidities and outcomes including pregnancy-induced hypertension, risk of congenital anomalies, gestational diabetes mellitus, risk of preterm birth, stillbirth, SGA infants, LBW infants as well as more caesarean deliveries (331,332). Therefore, its association with infants' growth possibly occurred as a consequence of low birth weight or SGA status at birth, while some studies have also shown other disadvantages which persist until adulthood such as hypertension, obesity and diabetes (333).

Day to reach full feeds have been shown in many studies as an indicator of feeding progression and nutrient adequacy received by infants due to fewer feeding interruptions (334). The longer time taken to achieve full feeding at 150 ml/kg/d could be likely due to less mature preterm infants, SGA/being IUGR, lower

birthweight infants, and infants with many comorbidities as well as formula milk feeding use (334). Therefore, among UK infants, longer days taken to reach full feeds which had negatively impact growth could have been due to slow feeding increments as the majority of infants in this cohort were younger GA at <32 weeks and there was also a high prevalence of formula milk use in the unit. Formula feeding has been associated with a higher risk for feeding disruption due to suspicion or confirmed cases of NEC, and more associated feeding intolerance symptoms such as vomiting, abdominal distension, and bloody stools. As a result, more cautious and conservative formula milk feeding could have been applied in the unit as reported in other studies (335,336).

Finally, protein intakes and PER in the first 4 weeks of life in this cohort positively predicts the most variation in changes in WAZ which was also shown in many studies (330,337) particularly among cohort predominantly fed with formula milk (338). For a change in WAZ, previous studies showed that optimised nutritional protocol with protein intakes aimed at 3.8–4.4 g/kg/d (by end of week 1) showed improvement in the WAZ in the first 6 weeks of life with decreased cumulative protein deficits and less WAZ change between birth to discharge (41). Many other also reported slow growth occurred when protein intakes are considerably less than recommended requirements, even with energy intakes inclining to be closer to or above requirements (50). This is pertinent to this study where UK infants showed high cumulative protein deficits as well as inadequate protein intakes for the whole hospital stay for most infants, despite adequate energy intakes – leading to low PER and resulted in unsatisfactory growth outcomes in this cohort.

Therefore, even though formula milk was demonstrated in many studies to offer higher protein intakes than unfortified breast milk hence leading to better growth (77,339), 48% of infants in this cohort received a mix of formula milk and unfortified breast milk, with approximately 70% of calories were from formula milk alone, which

provides in a range of 2.0-2.6g protein/100ml milk versus 1.3-1.9 g protein/100ml unfortified breast milk or 2.5-3.1g protein per 100 ml fortified breast milk.

As compared to the local study that showed high rates of positive growth outcomes among <32 GA infants, a mean protein intake was provided based on their newly introduced protocol at 3.7g/kg/d during the first 2 weeks of life (range 2.0 –4.9 g/kg/d) (42), which led to changes in WAZ of −0.27 (95% CI −0.39 to −0.15) at 36 weeks. Comparing with this cohort for infants of the same GA, they received a much lower mean protein intake of approximately 2.9 g/kg/d on week 2 of life and had changes in WAZ of -1.43 (95% CI -1.69 to -1.17) from birth to discharge.

This showed that careful monitoring and consideration of protein intakes should be a continuous process practised in the neonatal unit, even in seemingly healthy infants to help in preventing growth failure at discharge.

## 2.6 CONCLUSION

This was an observational study designed to compare nutritional practices in feeding preterm infants in the neonatal unit of two countries and to assess the association between feeding practices and growth outcomes at discharge.

In this study, it was shown that in the Malaysian unit, 35% of the fall in changes in WAZ at discharge could be explained by an extended length of stay in the neonatal unit. This is expected from the observation that infants in this cohort generally had received the ‘optimal’ feeding interventions as recommended, leading to the dismissal of nutritional factors as predictors for their growth failure at discharge. While staying longer in the hospital could be explained with many factors that were easily hypothesised in this cohort such as lower birth weight and higher morbidities, the remaining 65% unexplained factors- could consists of the underlying combination of influences, possibly unmeasured or concealed under its small

sample size, which may or may not affecting the feeding intervention of the infants but could be affecting the growth of these infants.

On the other hand, nutritional factors – mainly protein and PER on week 1-4 of life and days took to full enteral feeding, in addition to the non-nutritional factors which are the length of stay, birthweight Z-score and mother's age were identified as the predictors that could explain 62% of the variation in changes in WAZ at discharge for the UK infants. This was in line with what has been analysed of these infants who were seen as generally healthier and had significantly better at-birth weight/weight Z-score as compared to the Malaysian infants, but possibly receiving less than recommended nutrients intakes.

In this study, we have shown that in a group of preterm infants with varying gestational ages, their growth outcomes at discharge might be affected by many factors, even when nutritional intakes were seemingly adequate. Infants with clinical conditions might need higher intakes than recommended and infants who were born with lower GA or lower birthweight might need more aggressive nutrition interventions. The common occurrence of nutritional deficits may be reduced by improving the energy and protein intakes as early as possible during the first weeks of life, even in extremely preterm infants. The use of PN and early EN with fortified breast milk or a combination practice of formula milk with fortified breast milk (versus unfortified breast milk only) seems to contribute to the improvement of nutritional supply in this study.

The accumulation of nutritional deficits should be accessed early in addition to the weekly intakes assessment, as the nature and amount of the deficits differ between infants and units and what is rate-limiting in one infants/unit may not be rate-limiting in another. Nevertheless, it does emphasise the importance of controlling for non-nutritional factors if the effects of nutritional intakes and feeding practices were to be

focused on in future studies. Frequent monitoring and careful evaluations of nutritional intakes and growth in the neonatal units are necessary to identify the additional needs of these infants, even in the apparently 'healthy' infants. Further work is also required to determine optimal nutritional practices for a heterogenous group of preterm infants particularly those with SGA, IUGR, group of extremely preterm, late preterm, or even those with common prematurity-related medical conditions including IVH, BPD and PDA. Identification of personalised nutrition requirements for many of these conditions could help in avoiding impaired growth during hospital admission and also after hospital discharge.

## 2.7 STRENGTHS AND LIMITATIONS

The strengths of this study are that it is a two-centred cohort study with detailed nutritional intake and growth data collected prospectively. This study has assessed the common nutritional practices in the units of two different countries – which clearly had distinct differences in terms of the subject populations and their birth characteristics, feeding practices as well as neonatal unit policy and management.

Variations in nutritional practices have long been observed to not only occur between countries but also within the same country or even in the same hospital within a different level of neonatal care (267) and should be taken as a demonstration of the different feeding approaches or alternatives rather than an exact comparative analysis of these hospitals. However, preterm infants included in this study were all less than 34 weeks GA indicating the strongest criteria for a group of preterm infants who are commonly admitted to a neonatal unit after birth.

As for nutrition protocols, some of the feeding practices differences that were expected from the planning phase of the study such as PN regimen and types of formula milk and BMF products use were noted and calculations were carefully

done with the incorporation of these differences. The nutritional protocols used in these two units were based on similar international guideline but were applied differently perhaps due to differences in patient characteristics and cultural differences making such comparisons an interesting area of study.

Additionally, the nutritional intakes demonstrated in this study were not intended intakes, rather they were actual intakes that were recorded daily in the hospital system with very few missing data.

This study is limited by the nature of an observational study in which the associations between nutrition and growth do not prove causation. In addition, with multiple testing and small sample size in this study, findings should be interpreted with caution. It is important to take into consideration that the discharge pathway of an infant in the neonatal unit could be circular, where feeding practices could be affecting the growth of an infant, and on the other hand, growth, particularly weight gain and could also affect the feeding plans and ability to be discharged early.

On the other spectrum of the analysis, the use of changes in WAZ as a primary outcome in this study should also be discussed. In this study which involves a wide variation of gestational age of 25 to 33 weeks, WAZ is deemed to be the most suitable in the analysis as it takes account both GA and gender. The other most frequently used method in calculating weight gain velocity or growth is by using g/kg/d according to the Patel exponential model (333), although the method of its calculation is debatable as the rapid early growth seen in preterm infants certainly does not consistently follow an exponential trajectory. As the aim of the nutritional management of preterm infants is to support a growth trajectory which mimics the fetal growth, having a standard assessment method that could quantify the growth is thus crucial for the clinical care of these infants.

However, realistically in clinical practice, the decision to discharge infants is usually based on the specified criteria such as used in both units in this study – which are weight of at least 1800g, not needing any additional medical support, and fully milk fed. Usual practise at discharge does not require infants to have thorough investigation based on changes in WAZ from birth. This means that for this study, there is high possibility that many infants were routinely discharged home with underachieved WAZ as clinicians do not have the authority to withhold the discharge if all the specified criteria are deemed to be 'satisfactory'. On the other hand, because of these discharge criteria, there were also some infants who had to stay longer in the unit due to health factors and were discharged with positive changes in WAZ. Therefore, as there is currently no clear consensus exists regarding the methods suitable to quantify growth among preterm infants or even the standard cut-off for WAZ, findings of this study should be interpreted with adequate clinical knowledge on the importance of preventing growth failure in the unit and providing optimal feeding regimen for these infants.

Moreover, some of the data collection processes in this study can be improved. For example, the record of clinical conditions was not graded, and the severity of the conditions was not defined specifically. The use of scores such as Score for Neonatal Acute Physiology or Clinical Risk Index for Babies (CRIB/ CRIB II) (340) score that signifies the illness severity and predict the mortality would be convenient to distinguish those who were critically ill and those who had conditions but were generally stable. However, it should also be noted that there was also a low incidence of some of the most severe comorbidities including NEC, ROP and PVL among infants in this study that limited the power of the study to further identify associations of these conditions with growth at discharge. Therefore, 'sicker' infants were categorised as the variable with any of the conditions recorded for ease in analysis in this study.

Other than that, maternal medical history or maternal characteristics are also other important data items that would be helpful to have in this study. This could include maternal factors such as ethnicity, maternal BMI, nutritional status, smoking history as well as the medical history of chronic hypertension and diabetes as these are found to be associated with infants' outcomes in many studies (332,341).

As in many observational studies, all weight and HC measurements were performed in the respective units, possibly by different people taking care of the infants on a particular shift, which might reduce the homogeneity in the measurements. However, with more than 1000 measurements (i.e. for weight) taken, the effects of potential measurement errors may be lessened. For length measurement, as it is not a routine practice for it to be measured in the UK unit, the comparison was not done for this study, except for the measurements at birth. In terms of volumes of milk feeds recorded in this study, it is also prone to data or recording error, especially when involving the use of bottle feeding as the accurate volumes might not be precisely recorded if some feedings were not fully consumed ( i.e. unfinished/reflux). Besides, as mentioned in the methodology section, there was also no record of direct breastfeeding in this study – although measures have been taken to ensure the analysis of intakes can be estimated as much as possible.

In addition, as already described, the predominant use of expressed breast milk in this study especially in the Malaysian cohort means that the enteral energy and macronutrient intakes from breast milk were estimates using the best available reference (82) and so may not reflect the true nutritional composition of the milk received by each individual infant. The human milk analyser would be useful to have for larger studies.

Lastly, the use of the Fenton growth chart in this study in assessing growth outcomes of infants was done in the assumption that this is the best available chart

to use as a reference for both countries due to it being more recent and covers larger data for infants from many countries. It is also routinely used in many neonatal units including Malaysia. However, it is known that this chart may not represent the Asian population as much as it was constructed based on mostly a Caucasian population (287), which could also lead to higher SGA infants and lower weekly weight-for-age Z-score measurements classified in the Malaysian unit. Studies showed that there were significant deviations in the assessments of growth depending on the growth charts used (342,343).

Therefore, for future studies, the comparison of growth outcomes in infants using different growth charts such as INTERGROWTH-21, the UK-WHO Neonatal and Infant Close Monitoring Chart or local ethnicity-based growth chart (if available) could be attempted.

Admission to the neonatal units poses a highly challenging situation where barriers to receiving breast milk feeding might be more apparent due to factors such as frequent mother-infant separation as well as limited contacts between mother and infants due to visitation policy or clinical conditions of the infant. Therefore, in the next chapter, the prevalence of breastfeeding in the neonatal units is explored, taking into consideration the impact of visiting restrictions imposed during the recent COVID-19 pandemic.

# CHAPTER 3: THE PREVALENCE OF BREAST MILK FEEDING AMONG INFANTS ADMITTED TO THE NEONATAL UNITS DURING ADMISSION AND AT DISCHARGE

## 3.1 INTRODUCTION

It is well documented that breast milk feeding is the optimal type of nutrition for infants. Breast milk has been shown in RCTs and cohort studies to offer significant, dose-dependent short- and long-term benefits, such as the decreased risk of necrotising enterocolitis (NEC) and severe infections (70) as well as better neurodevelopmental outcomes (66,67).

It is recommended that infants initiate breastfeeding within an hour of birth (18) with immediate and uninterrupted skin-to-skin practice to facilitate the early and successful initiation of breastfeeding (344). Additionally, avoiding mother-infant separation and supporting maternal caregiving capability could also be very helpful in ensuring breastfeeding success as well as good maternal and infant health outcomes (263). On the contrary, factors such as separation of mother and infant, illness of the infants and mothers, multiple births, extended hospital stay, maternal anxiety and stress, maternal struggles to produce milk, and lack of breastfeeding support and early provision of additional foods or fluids were among issues identified that may be detrimental to breastfeeding in the neonatal unit (114,263).

Since December 2019, the infection of a novel beta-coronavirus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes coronavirus or COVID-19, has spread worldwide. The World Health Organization (WHO) on 11 March 2020 (257) declared the pandemic a public health emergency and, since then, ~6 million cases have been detected in the UK with ~131,000 deaths recorded as of the date (258). Due to the pandemic, there were heightened concerns over

how COVID-19 may affect pregnant and recently delivered women and newborn infants. At the time of writing, current evidence showed that the transmission of COVID-19 via vaginal birth to be unlikely (345–348). As for the vertical transmission, although there were 28 cases reported for its possibility for the transmission through this route, due to lack of virological testing at birth or in the first 12 hours of life, no cases reported have met the proposed testing for virus detection to confirm definite vertical transmission which leads to the unproven conclusion (349).

In addition, currently, there is no evidence of possible infective COVID-19 in human milk (264,350,351), while there are emerging reports of COVID-19 specific immunoglobulin found in infected mother's breast milk (264,352,353). A recent study also suggested that mothers who have been vaccinated against COVID-19 were found to produce antibodies to this virus in breast milk that may be protective for infants (354).

Additionally, ever since the early COVID-19 pandemic, many studies have demonstrated that neonatal COVID-19 infection is uncommon, and even when infected, it was rarely symptomatic (259,260,355). A systematic review also highlights that the rate of neonatal infection is no greater when the baby is born vaginally than by caesarean section, was breastfed rather than given formula milk or allowed contact with the mother rather than isolating after birth (349).

However, because of this pandemic, most hospitals around the world including in the UK have employed many immediate health service changes in the neonatal unit since the start of the pandemic in March 2020. There are five commonly used guidelines in the neonatal units for the management of infants of mothers with suspected or confirmed COVID-19 infection which were from WHO's *Clinical Management of Severe Acute Respiratory Infection (SARI) when COVID-19*

*Disease is Suspected: Interim Guidance* (WHO guidance) (356), the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, and Royal College of Paediatrics and Child Health (UK): *Coronavirus (COVID-19) Infection in Pregnancy: Information for Healthcare Professionals* (RCOG guidance) (357), the Chinese Expert Consensus : *Perinatal and Neonatal Management for the Prevention and Control of the 2019 Novel Coronavirus Infection* (China Consensus guidance) (358), the US Centers for Disease Control and Prevention: *Interim Considerations for Infection Prevention and Control of Coronavirus Disease 2019* (*COVID-19) in Inpatient Obstetric Healthcare Settings* (USCDC guidance) (359) and the American College of Obstetrics and Gynaecology : *Novel Coronavirus 2019* (*COVID-19): Practice Advisory* (ACOG guidance) (360).

However, these documents were contradictory in some aspects in which the China Consensus, USCDC and ACOG recommend isolation of mothers-infant dyads immediately after delivery and require impediments to direct breastfeeding so formula or expressed breast milk feeding is preferred, and possibly no contact should be made with the mother for 14 days or at least 7 days from the onset of the symptoms to avoid possible perinatal transmission.

On the contrary, the WHO and RCOG recommend infants even from suspected or confirmed COVID-19 mothers to be fed according to the standard infant feeding recommendations outlined in the *Global Strategy for Infant and Young Child Feeding* (18). This includes having skin-to-skin time with their mothers after birth, starting breastfeeding within 1 hour of birth, and all-day rooming-in with their mothers to encourage breastfeeding.

It was however recommended to practice respiratory hygiene during feeding such as wearing a mask and wash hands before and after touching the baby and routinely clean and disinfect surfaces they have contacted to avoid postnatal or

environmental transmission (361). WHO also suggested that “mothers should not be separated from their infants unless the mother is too sick to care for her baby”. The recommendation recognised that the severity of COVID-19 infections is much lower in infants and the protective benefits of breastfeeding against infections outweigh its unsupported risk.

At the neonatal unit level, some of the common recommendations translated from these guidelines are visiting hours restrictions in the neonatal unit (no visitor, mothers only or one parent only, once a day or with hours restriction or unlimited duration), complete mothers/infants separation and isolation or room-sharing at a specified distance/time, avoidance of skin-to-skin contact or requiring washing of mothers’ chest before skin-to-skin or breastfeeding (263). The use of face masks and personal protective equipment (PPE) was also required. The restrictions however differ considerably depending on local area/country infection rates, accessibility of PPE and the structure and layout of the neonatal unit (362).

In a study that included a review of 17 countries guidelines (363) have also shown that some countries/hospitals made immediate changes based on the early guidelines published such as separation of infants from mothers with suspected or confirmed Covid-19 and even avoidance of any breast milk feeding altogether especially during the early pandemic, although some have revised their position after some time (261,262).

In the UK specifically, the early national guidance in March 2020 relating to visitation policies in neonatal units was limited, showing the lack of evidence at that time. However, many individual neonatal units have directed that most hospital departments should not allow any visitors with a few exceptions for parents with a baby/child in the hospital. However, infants’ separation from mothers with confirmed or suspected COVID-19 was not advocated and breastfeeding was not discouraged

with the recommendation to practice proper hygiene (357). In December 2020, NHS England released a statement in alignment with the statement from RCPCH and the British Association of Perinatal Medicine (BAPM) which asserts that "parents are partners in care and should not be considered visitors" (364) to promote less restrictive access for parents to the neonatal units. This was also in line with the continuous assertions from organisations such as Bliss baby charity and UNICEF UK (265,365) which started in April and May 2020 on parental access, relaxing the visiting restrictions and encouragement on the continuation of breastfeeding.

However, with the overlapping and various guidelines and recommendations all around the world and within a country's hospital network, expectedly many health workers and local people are puzzled about the most appropriate infant feeding practice (366). These changes have been shown to have reduced or even stopped the mother-baby contact in some circumstances, which might impact breastfeeding practice (265). This is concerning as skin-to-skin contact is known to have physiological as well as psychological advantages for all infants (344) regardless of duration. In neonatal units, the practise of kangaroo care for preterm and sick infants is shown to be associated with reduced mortality and improved health outcomes (367).

In addition, the uncertainties and gaps in the evidence regarding breastfeeding during this pandemic have also been exploited by the breast milk substitute industry in promoting their products (368,369). All of these factors might be hypothesised to affect the initiation and successful continuation of breastfeeding in neonatal units during admission as well as at discharge.

Therefore, in this study, I aim to analyse the prevalence of breast milk feeding during admission and at discharge from a neonatal unit in the UK, comparing three

time periods - before the pandemic started, during the initial months of the pandemic and finally, the most recent months.

## 3.2 STUDY OBJECTIVES

1. To describe and compare the characteristics of infants who received any breast milk during admission and at discharge with those who did not receive any breast milk during the study period.
2. To describe the prevalence of breast milk feeding in one UK neonatal unit during admission and at discharge, before and during the COVID-19 pandemic.
3. To explore the effects of the implementation of visiting restrictions due to the COVID-19 pandemic on the prevalence of breast milk feeding in infants admitted to the neonatal unit.

## 3.3 METHODOLOGY

### 3.3.1 Study design

Retrospective cohort study using operational National Health Service (NHS) data from the BadgerNet platform for the period of 2017 until 2020.

#### 3.3.1.1 Introduction to BadgerNet

In 2003, it was recognised that an organised system was needed in the UK for reporting neonatal activity that would allow clinical data transfer between hospitals/units and provide reports of activity and clinical outcomes for statistics and audit purposes. In 2005, a national neonatal electronic patient record (EPR) was introduced with the NHS approved supplier, Clevermed Ltd, providing a web-based data capture platform known as BadgerNet. Since then, BadgerNet has expanded

as a platform for patient data management and records that can be shared across neonatal and maternity units to plan services and record activity (370).

Based on the Clevermed Ltd website (www.clevermed.com), in terms of its direct services, BadgerNet consists of:

i) BadgerNet Maternity

ii) BadgerNet Neonatal

iii) BadgerNet PICU and HDU

BadgerNet Maternity holds records which include antenatal, intrapartum, and postnatal events, as well as full risk assessments, management plans, referrals, and all contacts. It links with all BadgerNet maternity and neonatal units across the UK.

BadgerNet Neonatal hold records for each infants' admission or transfer to a neonatal unit and forms a single, continuous care record for neonatal and paediatric care for all infants within neonatal services. This record also links with BadgerNet Paediatric Intensive Care (PIC), Paediatric High Dependency Care (HDC), and Paediatric Oncology. This is available in two versions: i) as a Clinical summary system which records basic events during the hospital admission, and ii) as a full, paperless EPR.

A summary system permits daily recording of events within the unit including statutory data collection and reporting. Essential clinical summary data can be entered into this system which include admission / discharge details and reports, pregnancy and labour/delivery details, daily clinical summary form, as well as ad-hoc events. In addition, any national or international audit data sets can be made available and updated from this system as preferred.

BadgerNet EPR allows real time recording of all daily events in the neonatal unit and it extends the clinical summary version. Its core elements include ad hoc event forms for all events within the unit, fluids charting and full lines and infusions management, drug charting, results interfaces and charting, interfaces to patient monitors with real time trend data recording, nurse charting, as well as clinical and nurse handover documentation.

Data from BadgerNet Neonatal are extracted and used currently in forming the National Neonatal Research Database (NNRD) held at the Neonatal Data Analysis Unit (NDAU) which I used in this thesis (Chapter 4 : Gastro-oesophageal Reflux Disease (GORD) and anti-reflux medication use among preterm infants in neonatal units in England and Wales) as well as for the annual neonatal audit known as National Neonatal Audit Program (370).

Lastly, BadgerNet PICU and HDU is able to record all events within a paediatric intensive care or high dependency unit and forms part of the single care record for infants and children. This system can also link to BadgerNet Neonatal and Maternity.

### 3.3.2 Ethical approval

For this retrospective cohort study, ethical approval was not required as it was approved as an audit and service evaluation project by the hospital care group management. Data were acquired as per of the participating NHS Trusts' approved clinical governance pathways. Clinical team members (my supervisors) registered the study as clinical audits at their respective NHS Trusts and received approval for using the data for this study. As per the approval, deidentified data files were transferred to the University of Nottingham for analysis. The data were acquired from routinely collected electronic patient records (EPR) using the BadgerNet

(Clevermed Ltd.) platform. This EPR is used for data collection for clinical care, governance and research. Parents are informed about the collection and use of these data upon their baby's admission to the neonatal unit and any parent who does not want their baby's data to be included can opt out. The same data are acquired, at the national level, for forming the National Neonatal Research Database.

### 3.3.3 Study setting

The neonatal unit at Royal Derby Hospital is a local neonatal care unit (Level II) which cares for preterm infants born >25 weeks gestational age and infants who need care immediately after birth. The unit has 24 neonatal cots and caters to approximately 6000-7000 birth per year. More immature infants and those requiring surgical or other specialised care are transferred to appropriate centres. This neonatal unit is currently at Stage 1 accreditation for the Baby-Friendly units which was awarded in 2018 showing that policies and procedures to support the implementation of the BFHI standards have been created and assessed to be adequate (309).

#### 3.3.3.1 Neonatal unit protocol before the pandemic

Before the pandemic, all the mothers/parents were allowed unlimited access to visit and were able to feed their babies throughout the day. Direct breastfeeding is encouraged and there is support provided in the unit by the nurses and lactation nurses if needed. For infants who were on tube feeding or bottle feeding, expressed breast milk is the preferred milk and usually provided and sent by mothers to the neonatal unit and is stored in the unit and warmed at the feeding times.

#### 3.3.3.2 Neonatal unit protocol during the pandemic

After the start of the lockdown in 23rd of March 2020, only one of the parents were allowed to visit their babies once a day. Either one of them was able to choose to stay all day or for a short period of time, but there should be no swapping or return in the same day. All parents were required to wear face masks, gloves, disposable clothing, and to practice social distancing in the unit and proper hand sanitising. Rooming-in and breastfeeding were allowed as usual. Mothers who are suspected or confirmed to have COVID-19 will not be able to go onto the unit until they have tested negative or until 10 days after the onset of their symptoms and they are symptom-free, but they can continue sending expressed breast milk to the unit. If mothers/parents have any symptoms of COVID-19, they should self-isolate for 10 days following NHS guidelines and not come to the neonatal unit until a negative test has been confirmed and they are symptom-free. The visitation policy was gradually eased in August 2020 when there was unrestricted access to mothers, but partners can visit once a day for any duration. Partners may choose to stay all day or for a short period of time, but there should be no swapping or return on the same day.

### 3.3.4 Study participants

#### 3.3.4.1 Identification of study cohort

The initial dataset contained data on all infants with GA of 23 to 42 weeks admitted from 1 January 2017 to 31 December 2020. A set of inclusion and exclusion criteria as listed below were applied to derive the final dataset.

#### 3.3.4.2 Inclusion criteria

- All infants who were born and admitted to the neonatal units at RDH from 1 January 2017 to 31 December 2020

- Only have one episode of care (i.e. they were not transferred elsewhere as part of their care)
- Discharged to home/social care/ward from the neonatal unit

#### 3.3.4.3 Exclusion criteria

- Length of stay in the unit of less than 24 hours

### 3.3.5 Data Extraction Procedure

#### 3.3.5.1 Data extraction

Table 3.1 to Table 3.3 shows the demographic, diagnoses and outcome variables which were extracted or derived from the raw downloaded BadgerNet Clinical summary data files. These were used to build a study dataset containing information for all eligible infants. For information on diagnosis/morbidities of infants, a list of co-morbidities and congenital anomalies which might affect the overall condition and feeding of infants were identified (371,372).

These were extracted from the variables “diagnosis during stay” and “principal diagnosis at discharge” fields in the BadgerNet. Infants who have had any record of the diagnoses listed, either from admission or discharge data were considered to have had the diagnosis.

**Table 3.1: Data extracted for demographic information**

| Variable | Data extraction and categorisation |
|---|---|
| Sex | Male; female |
| Birthweight and weight at discharge | In grams, and categorised as follows:<br>• Birthweight category: Extremely low birth weight (ELBW, <1000g), very low birth weight (VLBW,<1500g), low birth weight (LBW,<2500), normal birth weight (NBW, ≥2500g)<br>• Weight-for-age Z-score ( birth and at discharge) and birthweight status (small-for gestational, (SGA), appropriate-for-gestational age (AGA) and large-for-gestational age (LGA)) |
| Gestational age (GA) at birth | In completed weeks, and categorised as follows:<br>• <28 weeks (extremely preterm infants), 28-31 weeks (very preterm infants), 32-36 weeks (moderate to late preterm infants) and 37-42 weeks (term infants) |
| Episode number | Used to determine number of episodes of care |
| Month and year of birth | Combination of month/year of birth |
| Month and year of admission | • Combination of month/year of admission<br>• Determine period of pre-pandemic and during pandemic |
| Month and year of discharge | • Combination of month/year of discharge<br>• Determine length of stay in the neonatal unit from time of admission to time of discharge |
| Mother's postcode | Determine Index of Multiple Deprivation (IMD) quantile, from 1 (most deprived) to 5 (least deprived) |
| Discharge destination | Categorised as follows:<br>• Home; transfer for further medical care; died before discharge; transfer to ward, social care. |

**Table 3.2: : Data extracted on infants' diagnoses and treatments which may affect feeding**

| Diagnoses | Type of diagnosis | Entries within BadgerNet data |
|---|---|---|
| Parenteral nutrition days (PN days) | Received PN for ≥ 14 days | "parenteral nutrition days" |
| Ventilation days | Received ventilation for more than 3 days | "ventilation days" |

| | | |
|---|---|---|
| Congenital anomalies (those deemed likely to affect the overall condition and feeding of infants) | Cleft lip or palate, Chiari malformation, Down syndrome, Congenital cardiac disease, Oesophageal atresia, Intestinal atresia, Hirschsprung disease, Gastroschisis, Biliary atresia, VATER syndrome, Edwards' syndrome, Pierre robin sequence/syndrome, Tetralogy of fallot, Anorectal malformation, Omphalocele, CHARGE syndrome, 22q11.2 Deletion syndrome, Micrognathia, Glossoptosis and Choanal atresia | "cleft lip or palate", "chiari", "down syndrome", "congenital cardiac disease", "oesophageal atresia", "intestinal atresia", "hirschsprung disease", "gastroschisis","biliary atresia","vater","edwards"," pierre robin","tetralogy of fallot","anorectal malformation","omphalocel e","charge sydrome", "deletion syndrome", "micrognathia", "glossoptosis", "choanal atresia" |
| Necrotising enterocolitis (NEC) (confirmed) | Necrotising enterocolitis | -"necrotising enterocolitis – confirmed" |
| Chronic lung disease | Chronic lung disease at 36 weeks GA | -"chronic lung disease at 36 weeks' gestation" |
| Hypoxic-ischemic encephalopathy (HIE) | Hypoxic-ischemic encephalopathy (HIE) | "hie grade" (all grades) |
| Intraventricular hemorrhage (IVH) | Intraventricular hemorrhage (IVH) grade 3 or 4 (severe) | "ivh grade 3"<br><br>"ivh grade 4" |
| Patent Ductus Arteriosus (PDA) | Patent Ductus Arteriosus (PDA) | "patent ductus arteriosus" |
| Sepsis (confirmed) | Confirmed sepsis | "anaerobic sepsis / septicaemia", "bacterial sepsis / septicaemia", "bacterial sepsis / septicaemia (other)", "candida sepsis / septicaemia", "confirmed bacterial sepsis", "e.coli sepsis / septicaemia", "extended beta lactamase coliform infection/sepsis", "group b streptococcal |

| | | |
|---|---|---|
| | | sepsis / septicaemia (gbs)", "listeria sepsis / septicaemia / disseminated", "sepsis-candida", "sepsis - confirmed bacterial (gram negative), "sepsis - confirmed bacterial (gram positive)", "sepsis - confirmed bacterial (streptococci b positive)",<br><br>, "sepsis - confirmed bacterial (streptococci positive)", "sepsis - e coli", "sepsis - klebsiella sp","sepsis - staph aureus", "sepsis / septicaemia - confirmed with +ve microbiology", "sepsis / septicaemia - specified - enterobacter sp.", "sepsis / septicaemia - specified - klebsiella sp.", "sepsis / septicaemia - specified - pseudomonas sp."), "staph. aureus sepsis / septicaemia", "staph. epidermidis sepsis / septicaemia (cons)", "staphylococcal sepsis / septicaemia", "streptococcal sepsis / septicaemia","toxic shock / sepsis syndrome" |

One summary variable was created to indicate sickness to an extent in which it may have affected breast milk feeding. This binary variable is coded as “1” (yes) if the infant had a record of any of these conditions: received PN for ≥ 14 days, ventilated for >3 days, any congenital anomalies listed, diagnosis of NEC, IVH grade 3/4, PDA, HIE, CLD, or confirmed sepsis.

**Table 3.3: Data extraction for outcome variables**

| Variables | Specification of outcomes | Entries within BadgerNet data |
|---|---|---|
| Breast milk feeding during admission | Received any breast milk during admission in the neonatal unit from enteral nutrition (expressed breast milk)/direct breastfeeding | "Received mothers milk during admission" |
| Breast milk feeding at discharge | Received any breast milk during at discharge from enteral nutrition (expressed breast milk)/direct breastfeeding | "Discharge milk"<br>"Discharge feed" |
| Exclusive breast milk feeding at discharge | Received only breast milk at discharge from enteral nutrition (expressed breast milk)/direct breastfeeding | "Discharge milk" |

### 3.3.6 Data analysis

Specific methods used to address the three study objectives are described below:

**Objective 1: To describe and compare the characteristics of infants who received any breast milk during admission and at discharge with those who did not receive any breast milk during the study period.**

For this objective, the infant and maternal basic and clinical characteristics were compared between i) infants who receive any breast milk during admission with those who did not receive any breast milk during admission; ii) infants who received exclusive breast milk at discharge with those who did not receive any breast milk at discharge. Descriptive statistics were used to describe the demographic characteristics of infants and mothers. Values were presented as numbers and

percentages for categorical data and for continuous variables, mean (± standard deviation, SD) was used for normally distributed data and median (inter-quartile range, minimum and maximum values) for non-normally distributed data. The Student-t test was used to compare normally distributed continuous variables between groups and the Mann-Whitney test for non-normally distributed variables.

**Objective 2: To describe the prevalence of breast milk feeding in the neonatal unit during admission and at discharge, before and during the COVID-19 pandemic.**

For this objective, the prevalence of breast milk feeding was shown by 30-day admission periods, defined as the 23rd day of one month to the 22nd day of the following month, to align with the date when national lockdown was implemented and visiting restrictions introduced on 23rd March 2020. The prevalence of three different outcomes was described: 1) any BM feeding during admission 2) any BM feeding at discharge 3) exclusive BM feeding at discharge, based on the specifications on Table 3.3 which include direct breastfeeding or the use of expressed breast milk.

**Objective 3: To explore the effects of the implementation of restrictions due to the COVID-19 pandemic on the prevalence breast milk feeding in infants admitted to the neonatal unit.**

For this objective, records of BM feeding during admission and at discharge were retrieved from the database and three distinct periods of restrictions were defined, which are:

i) period I: no restrictions (prior to 23rd March 2020). Unrestricted parental access to the neonatal unit.

ii) period II: restrictions were first implemented (23rd March 2020- 31st July 2020. Mothers/one parent/partner can visit once a day for any duration.

iii) period III: restrictions were gradually relaxed (1st August 2020 onwards). Unrestricted access to mothers, but partners can visit once a day for any duration.

Logistic regression was used to calculate odds ratios (ORs) to compare the prevalence of BM feeding for all three outcomes in periods II and III relative to period I. Adjusted ORs (AOR) were calculated adjusting for the following confounders specified *a priori*: GA group; birthweight category; sex; IMD quantile; and the binary variable indicating overall sickness.

Statistical analysis was performed using STATA 16.0 software (Stata Corp. College Station, TX).

#### 3.3.6.1 Descriptive analysis

Line graphs were used to describe the prevalence of any breast milk feeding during admission, at discharge and exclusive breast milk feeding at discharge. Each line graph shows breast milk feeding prevalence across the 30-day periods of admission which include a period before the pandemic/restrictions were implemented, during the initial implementation of restrictions due to the pandemic and when the restrictions were relaxed. This allows the overall trend over time in breast milk feeding prevalence to be observed and initial assessment of how outcomes differ between the three time periods.

Sensitivity analyses (SA) were also performed to determine the robustness of the primary outcomes in terms of the period of assessment and application of exclusion criteria by including all infants regardless length of stay and analysis of outcomes by 30-day period of discharge instead of admission.

#### 3.3.6.2 Regression analysis

A logistic regression analysis was conducted in order to observe the change in the odds of receiving breast milk after the implementation of restrictions in the neonatal unit (period II) and when the restrictions were relaxed (period III), as compared to the period before pandemic/restrictions (period I).

Three binary outcomes variables were analysed, which are: 1) received any breast milk feeding during admission; 2) received any breast milk at discharge; 3) exclusive breast milk feeding at discharge. An unadjusted logistic regression analysis was initially performed for all three outcomes, followed by adjusted logistic regression analysis.

The values were adjusted for GA group, birthweight category, received PN ≥2 weeks (prolonged), received ventilation ≥3 days, and had any of the conditions that indicate sickness: confirmed NEC, confirmed sepsis, HIE, IVH grade 3/4, and any listed congenital anomalies.

## 3.4 RESULTS

In this section, the population baseline data are presented first, which includes overall infant characteristics at birth and during admission, until discharge. This is followed by the main results which are presented according to the three objectives that are stated earlier.

### 3.4.1 Characteristics of the study population

Figure 3.1 below shows a flow chart of the included infants in the completed database analysis, which is based on the data extracted from BadgerNet. These infants were then excluded based on the exclusion criteria of the study, which then

leads to the final number of 1072 infants with complete data for analysis. Table 3.4 shows basic infant and maternal characteristics for the infants included in this study.

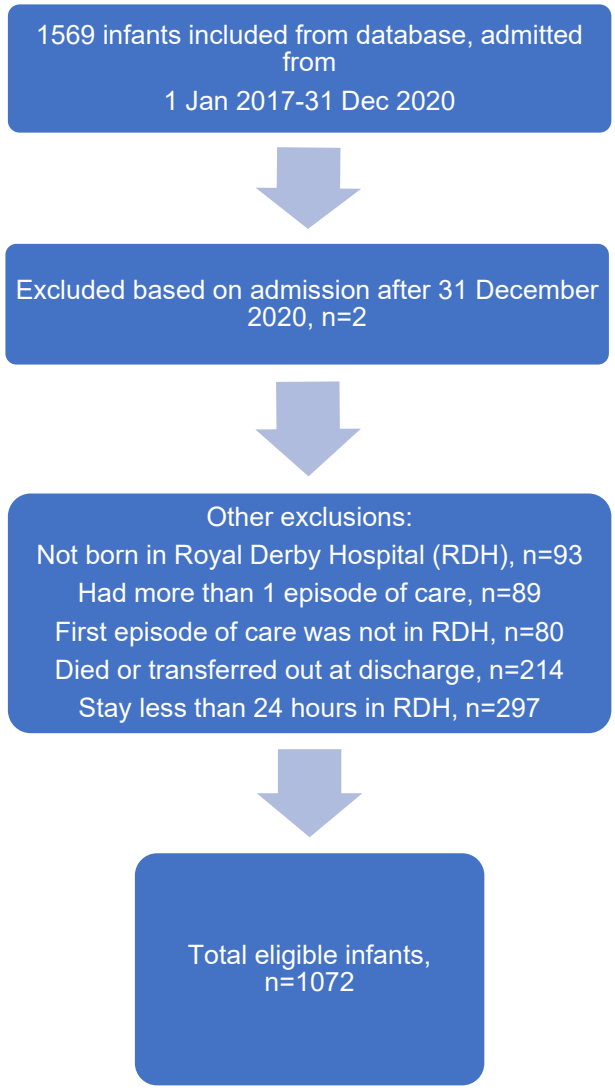



**Figure 3.1: Flow chart of included infants**

**Table 3.4: Infants and maternal characteristics**

| Variables, n (%) | All infants n=1072 |
|---|---|
| **Infants characteristics** | |
| Female | 626 (58.4) |
| Gestational age (weeks), median (IQR, range) | 35 (33-37,25-42) |
| Birthweight (g), mean (SD) | 2427 (861) |
| Weight-for-age Z-score at birth, mean (SD) | -0.16 (1.1) |
| Small-for-gestational age (SGA) | 142 (13.3) |
| Singleton | 900 (84.0) |
| Length of hospital stay (day), median (IQR, range) | 11 (3-21,1-134) |
| Received ventilation for ≥ 3 days | 42 (3.9) |
| Received parenteral nutritional for ≥14 days | 10 (0.9) |
| Received any breast milk during admission | 766 (71.6) |
| Received any breast milk at discharge | 513 (47.9) |
| Received only breast milk ( exclusive breast milk feeding) at discharge | 296 (27.6) |
| Discharge destination:<br>Home<br>Social care<br>Ward | <br>724 (67.5)<br>22 (2.1)<br>326 (30.4) |
| Postmenstrual age (PMA) at discharge (weeks), median (IQR, range) | 37 (36-38,33-47) |
| Weight at discharge, mean (SD) | 2610 (703) |
| Weight-for-age Z-score at discharge, mean (SD) | -0.98 (1.3) |
| Change in weight-for-age Z-score from birth to discharge | -0.82 (0.7) |
| **Clinical diagnosis** | |
| Necrotising enterocolitis (NEC) | 3 (0.3) |
| Sepsis | 27 (2.5) |
| Chronic lung disease | 28 (2.6) |
| Hypoxic-ischemic encephalopathy (HIE) | 15 (1.4) |
| Intraventricular haemorrhage (IVH) (Grade 3/4) | 4 (0.4) |
| Patent ductus arteriosus (PDA) | 43 (4.0) |
| Congenital anomalies* | 19 (1.8) |
| **Maternal characteristics** | |
| Maternal age (years), mean (SD) | 30 (6) |
| Index of Multiple Deprivation (IMD) quantile:<br>Q1(Most deprived)<br>Q2<br>Q3<br>Q4<br>Q5 (Least deprived)<br>Missing | <br>172 (16.0)<br>120 (11.2)<br>208 (19.4)<br>207 (19.3)<br>264 (24.6)<br>101 (9.4) |
| Type of delivery:<br>Caesarean<br>Vaginal birth<br>Missing | <br>581 (54.2)<br>449 (41.9)<br>42 (3.9) |

*Congenital anomalies are as listed in the methodology section of this study.

As shown in Table 3.4, almost 60% of infants included in this study were female, with median GA (IQR) of 35 (33-37) weeks, mean (SD) birthweight of 2427 (861) g and about 13% of these infants were SGA. The majority of infants (84%) were singletons with median (IQR) length of stay of 11 (3-21) days. The most common diagnosis recorded for included infants was a diagnosis of PDA (43%). Almost 70% of infants were discharged home and median (IQR) PMA at discharge was 37 (36-38) weeks. Approximately a total of 27% (n=292) of infants included were from a more deprived area with IMD quantile of 1 and 2 while about a total of 40% (n=471) of infants were from less deprived areas at IMD quantile of 4 and 5.

### 3.4.2 Descriptive Analysis

#### 3.4.2.1 Objective 1: What are the characteristics of infants who received any breast milk during admission and exclusive breast milk at discharge as compared to those who did not receive any breast milk?

From Table 3.4, it was described that 766 (71.6%) of infants were recorded to have received any breast milk feeding during admission, 513 (47.9%) received any breast milk feeding at discharge while 296 (27.6%) have received only breast milk (exclusive breast milk feeding) at discharge.

From these results, further analyses were performed to compare i) the characteristics of infants with recorded any breast milk feeding during admission to those with no record of breast milk feeding during admission (Table 3.5) and ii) infants who received exclusive breast milk feeding at discharge to those with no record of breast milk feeding at discharge (Table 3.6).

**Table 3.5: Characteristics of infants who received any breast milk and did not receive breast milk during admission**

| Variables, n (%) | Total infants, n= 1070 | | p-value |
|---|---|---|---|
| | Received any breast milk, n=766 | Did not receive any breast milk, n=304 | |
| **Infants characteristics** | | | |
| Female | 317 (41.4) | 129 (42.4) | 0.753 |
| Gestational age (weeks), median (IQR, range) | 34 (32-37, 25-42) | 36 (34-38, 29-42) | <0.001 |
| Birthweight (g), mean (SD) | 2317 (877) | 2698 (756) | <0.001 |
| Weight-for-age Z-score at birth, mean (SD) | -0.15 (1.0) | -0.17 (1.1) | 0.792 |
| Small-for-gestational age (SGA) | 98 (12.8) | 44 (14.5) | 0.465 |
| Singleton | 637 (83.2) | 261 (85.9) | 0.279 |
| Length of hospital stay (day), median (IQR, range) | 14 (5-27,1-134) | 5 (2-12,1-59) | <0.001 |
| Received ventilation for ≥ 3 days | 40 (5.2) | 2 (0.7) | 0.001 |
| Received PN for ≥14 days | 10 (1.3) | 0 (0.0) | 0.045 |
| Received any breast milk at discharge | 482 (62.9) | 30 (9.9) | <0.001 |
| Received exclusive breast milk at discharge | 287 (37.5) | 8 (2.6) | <0.001 |
| Discharge destination:<br>Home<br>Social care<br>Ward | <br>569 (74.3)<br>7 (0.9)<br>190 (24.8) | <br>154 (50.7)<br>15 (4.9)<br>135 (44.4) | <0.001 |
| Postmenstrual age (PMA) at discharge (weeks), median (IQR, range) | 37 (26-38, 33-47) | 37 (35-39, 33-42) | 0.435 |
| Weight at discharge, mean (SD) | 2568 (696) | 2717 (713) | 0.003 |
| Weight-for-age Z-score at discharge, mean (SD) | -1.07 (1.2) | -0.74 (1.3) | <0.001 |
| Changes in weight-for-age Z-score of ≥-1.28 | 185 (24.2) | 24 (7.9) | <0.001 |
| **Clinical diagnosis** | | | |
| Necrotising enterocolitis (NEC) | 3 (0.4) | 0 (0.0 | 0.275 |
| Sepsis | 24(3.1) | 3 (1.0) | 0.043 |
| Chronic lung disease | 28 (3.7) | 0 (0.0) | 0.001 |
| Hypoxic-ischemic encephalopathy (HIE) | 11(1.4) | 4 (1.3) | 0.880 |
| Intraventricular haemorrhage (IVH) (Grade 3/4) | 4 (0.5) | 0 (0.0) | 0.207 |
| Patent ductus arteriosus (PDA) | 41(5.4) | 2 (0.7) | <0.001 |
| Congenital anomalies* | 17 (2.2) | 2 (0.7) | 0.081 |
| **Maternal characteristics** | | | |
| Maternal age (years), mean (SD) | 31 (6) | 29 (5) | <0.001 |
| Index of Multiple Deprivation (IMD) quantile:<br>Q1(Most deprived)<br>Q2<br>Q3<br>Q4<br>Q5 (Least deprived)<br>Missing | <br>133 (17.4)<br>91 (11.9)<br>137 (17.9)<br>144 (18.8)<br>185 (24.1)<br>76 (9.9) | <br>39 (12.8)<br>28 (9.2)<br>70 (23.0)<br>63 (20.7)<br>79 (25.9)<br>25 (8.2) | 0.129 |
| Type of delivery:<br>Caesarean<br>Vaginal birth<br>Missing | <br>402 (52.5)<br>339 (44.3)<br>25 (3.3) | <br>177 (58.2)<br>110 (36.2)<br>17 (5.6) | 0.005 |

**Table 3.6: Characteristics of infants who received exclusive breast milk and did not receive any breast milk at discharge**

| Variables, n (%) | Total infants, n=1072 | | p-value |
|---|---|---|---|
| | Received exclusive breast milk n=296 | Did not receive any breast milk n=559 | |
| **Infants characteristics** | | | |
| Female | 122 (41.2) | 245 (43.8) | 0.463 |
| Gestational age (weeks), median (IQR,range) | 35 (33-37, 27-42) | 34 (33-37, 25-42) | 0.062 |
| Birthweight (g), mean (SD) | 2513 (849) | 2346 (858) | 0.007 |
| Weight-for-age Z-score at birth, mean (SD) | -0.08 (0.97) | -0.21 (1.1) | 0.089 |
| Small-for-gestational age (SGA) | 28 (9.5) | 87 (15.6) | 0.013 |
| Singleton | 264 (89.2) | 458 (81.9) | 0.005 |
| Length of hospital stay (day), median (IQR,range) | 10 (2-20, 1-76) | 12 (3-24, 1-134) | 0.042 |
| Received ventilation for ≥ 3 days | 11 (3.7) | 26 (4.7) | 0.523 |
| Received PN for ≥14 days | 0 (0.0) | 10 (1.8) | 0.021 |
| Received any breast milk during admission | 287 (97.3) | 284 (50.9) | <0.001 |
| Discharge destination:<br>Home<br>Social care<br>Ward | <br>196 (66.2)<br>0 (0.0)100 (33.8) | <br>384 (68.7)<br>22 (3.9)<br>153 (27.4) | 0.001 |
| Postmenstrual age (PMA) at discharge (weeks),median (IQR,range) | 37 (35-38, 33-42) | 37 (36-38, 33-47) | 0.729 |
| Weight at discharge, mean (SD) | 2603 (685) | 2598 (696) | 0.917 |
| Weight-for-age Z-score at discharge, mean (SD) | -0.94 (1.2) | -1.02 (1.2) | 0.332 |
| Change in weight-for-age Z-score of ≥-1.28 | 77 (26.0) | 93 (16.6) | 0.001 |
| **Clinical diagnosis** | | | |
| Necrotising enterocolitis (NEC) | 0 (0.0) | 3 (0.5) | 0.207 |
| Sepsis | 5 (1.7) | 16 (2.9) | 0.292 |
| Chronic lung disease | 3 (1.0) | 23 (4.1) | 0.012 |
| Hypoxic-ischemic encephalopathy (HIE) | 6 (2.0) | 5 (0.9) | 0.162 |
| Intraventricular haemorrhage (IVH) (Grade 3/4) | 0 (0.0) | 4 (0.7) | 0.145 |
| Patent ductus arteriosus (PDA) | 9 (3.0) | 26 (4.7) | 0.258 |
| Congenital anomalies* | 2 (0.7) | 8 (1.4) | 0.328 |
| **Maternal characteristics** | | | |
| Maternal age (years), mean (SD) | 31 (5) | 29 (6) | <0.001 |
| Index of Multiple Deprivation (IMD) quantile:<br>Q1(Most deprived)<br>Q2<br>Q3<br>Q4<br>Q5 (Least deprived)<br>Missing | <br>59 (19.9)<br>46 (15.5)<br>56 (18.9)<br>56 (18.9)<br>49 (16.5)<br>30 (10.1) | <br>69 (12.3)<br>57 (10.2)<br>107 (19.1)<br>112 (20.0)<br>166 (29.7)<br>48 (8.6) | <0.001 |
| Type of delivery:<br>Caesarean<br>Vaginal birth<br>Missing | <br>174 (58.8)<br>113 (38.2)<br>9 (3.0) | <br>233 (41.7)<br>302 (54.0)<br>24 (4.3) | 0.512 |

Based on Table 3.5, infants who received any breast milk during admission were born at earlier GA, had lower birthweight and stayed in the hospital for a significantly longer time at median of 14 days vs 5 days and had older mothers. More of these infants also were showed to have received ventilation for ≥ 3 days, PN for ≥ 14 days and continued to receive any breast milk and were exclusively breast milk fed at discharge as compared to infants who did not receive any breast milk during admission. More infants who received breast milk also were shown to have been diagnosed with clinical conditions such as sepsis, chronic lung disease, hypoxic-ischemic encephalopathy (HIE) and patent ductus arteriosus (PDA).

At discharge, infants who received any breast milk had lower weight and weight Z-score and more of these infants had changes of weight-for-age Z-score of ≥-1.28 indicative of growth failure as compared to those who did not receive any breast milk.

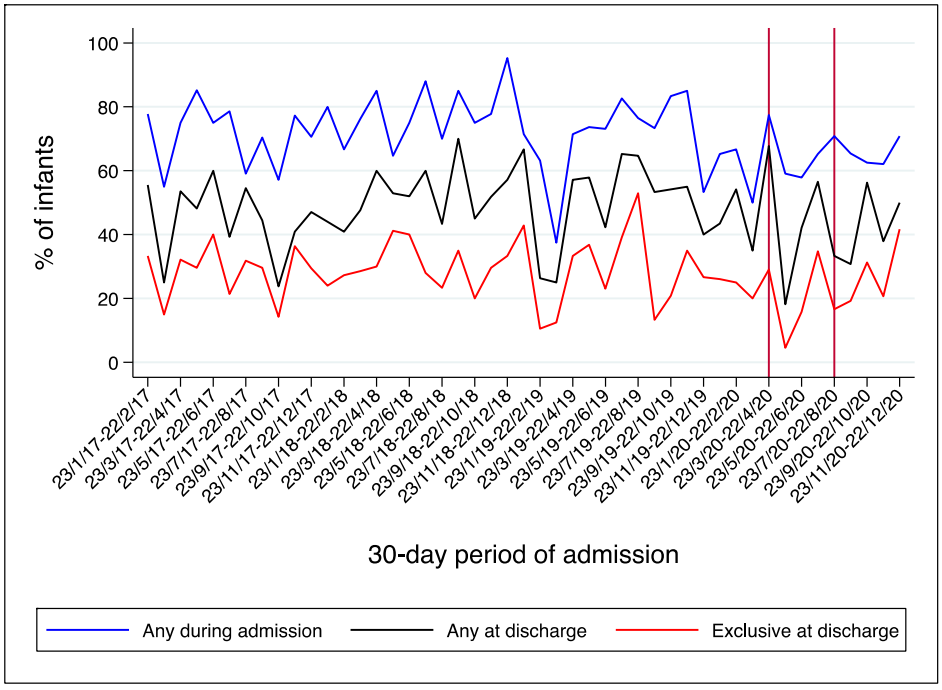
From Table 3.6, it shows that infants who received exclusive breast milk and did not receive any breast milk at discharge were of similar GA at birth. However, infants who received exclusive breast milk were heavier at birth, fewer of them were SGA, had older mothers, did not receive prolonged PN of ≥ 14 days during admission and expectedly most of them (97%) received any breast milk during admission. Fewer infants who received exclusive breast milk at discharge were recorded to have clinical diagnoses during admission as compared to those who did not receive any breast milk at discharge.

At discharge, infants who received exclusive breast milk had similar weight and weight Z-score with those who did not receive any breast milk, but higher percentage of these infants had changes of weight-for-age Z-score of ≥-1.28 indicative of growth failure as compared to those who did not receive any breast milk at discharge. The assessment of odds ratio to show the probability of receiving

breast milk in between groups were not attempted for this objective due to the relatively small sample size and possibly large number of confounders.

#### 3.4.2.2 Objective 2: How was the prevalence of breast milk feeding during admission and at discharge from 2017 to 2020, specifically before the COVID-19 pandemic and during COVID-19 pandemic?

Figure 3.2 shows the prevalence of breast milk feeding in the neonatal unit during admission, at discharge and exclusive breast milk feeding at discharge from 2017 to 2020 which includes a period of pre-pandemic and during early COVID-19 pandemic, followed by Table 3.7 which shows the percentages for each period.




Red vertical lines indicate a period when the restrictions in the neonatal unit were first implemented (period II)

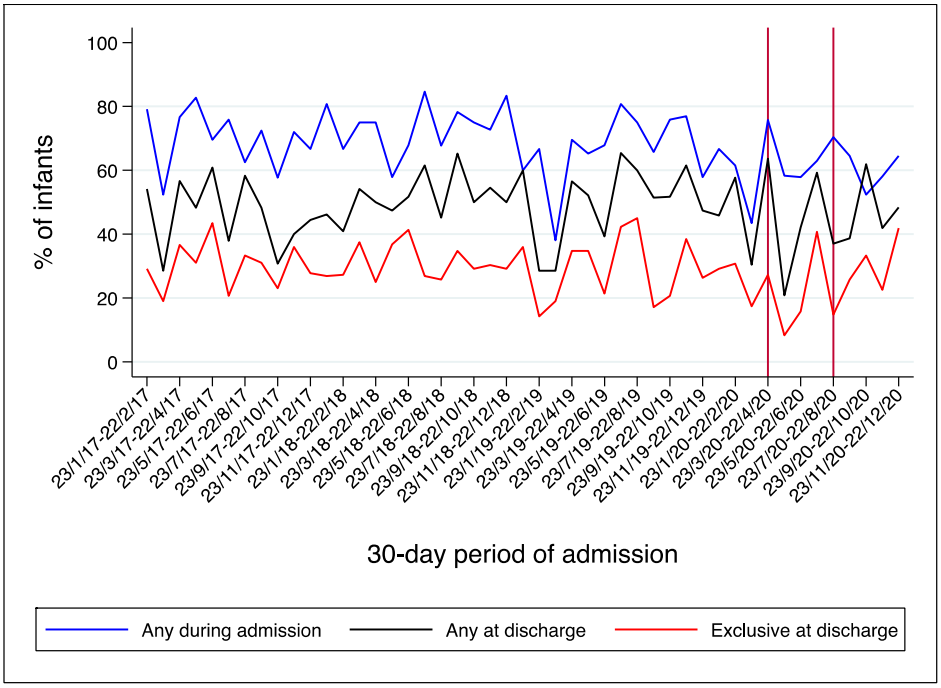
**Figure 3.2: Prevalence of breast milk feeding by 30-days period of admission (exclusion based on length of stay of <24 hours)**

**Table 3.7: Prevalence of breast milk feeding by 30-days period of admission**

| Period of admission | Total infants per period | Any breast milk during admission (%) | Any breast milk at discharge (%) | Exclusive breast milk at discharge (%) |
|---|---|---|---|---|
| 23 Jan-22 Feb 2017 | 18 | 78 | 56 | 33 |
| 23 Mar- 22 Apr 2017 | 28 | 75 | 54 | 32 |
| 23 May- 22 Jun 2017 | 20 | 75 | 60 | 40 |
| 23 Jul- 22 Aug 2017 | 22 | 59 | 55 | 32 |
| 23 Sept- 22 Oct 2017 | 21 | 57 | 24 | 14 |
| 23 Nov- 22 Dec 2017 | 17 | 71 | 47 | 29 |
| 23 Jan-22 Feb 2018 | 22 | 67 | 41 | 27 |
| 23 Mar- 22 Apr 2018 | 20 | 85 | 60 | 30 |
| 23 May- 22 Jun 2018 | 25 | 75 | 52 | 40 |
| 23 Jul- 22 Aug 2018 | 30 | 70 | 43 | 23 |
| 23 Sept- 22 Oct 2018 | 20 | 75 | 45 | 20 |
| 23 Nov- 22 Dec 2018 | 21 | 95 | 57 | 33 |
| 23 Jan-22 Feb 2019 | 19 | 63 | 26 | 11 |
| 23 Mar- 22 Apr 2019 | 21 | 71 | 57 | 33 |
| 23 May- 22 Jun 2019 | 26 | 73 | 42 | 23 |
| 23 Jul- 22 Aug 2019 | 17 | 76 | 65 | 53 |
| 23 Sept- 22 Oct 2019 | 24 | 83 | 54 | 21 |
| 23 Nov- 22 Dec 2019 | 15 | 53 | 40 | 27 |
| 23 Jan-22 Feb 2020 | 24 | 67 | 54 | 25 |
| 23 Mar- 22 Apr 2020 | 31 | 77 | 68 | 29 |
| 23 May- 22 Jun 2020 | 19 | 58 | 42 | 16 |
| 23 Jul- 22 Aug 2020 | 24 | 71 | 33 | 17 |
| 23 Sept- 22 Oct 2020 | 16 | 63 | 56 | 31 |
| 23 Nov- 22 Dec 2020 | 24 | 71 | 50 | 42 |

In general, there were fluctuations in the prevalence of breast milk feeding at discharge and exclusive breast milk feeding at discharge in the early COVID-19 pandemic from the period of 23rd March 2020-August 2020 though the rate of prevalence feeding at admission was quite stable. However, there were similar falls in the prevalence of breast milk feeding for all three outcomes observed in January 2019-April 2019 with no apparent explanations. From all the three outcomes analysed, the prevalence of breast milk feeding during admission was consistently higher than the rate of breast milk feeding at discharge and exclusive breast milk feeding at discharge across the period of admission. From Figure 3.2, the breast milk feeding rates are assessed in comparison to Figure 3.3 which included all infants regardless of length of stay and Figure 3.4 which showed the prevalence based on period of discharge, as a sensitivity analysis.

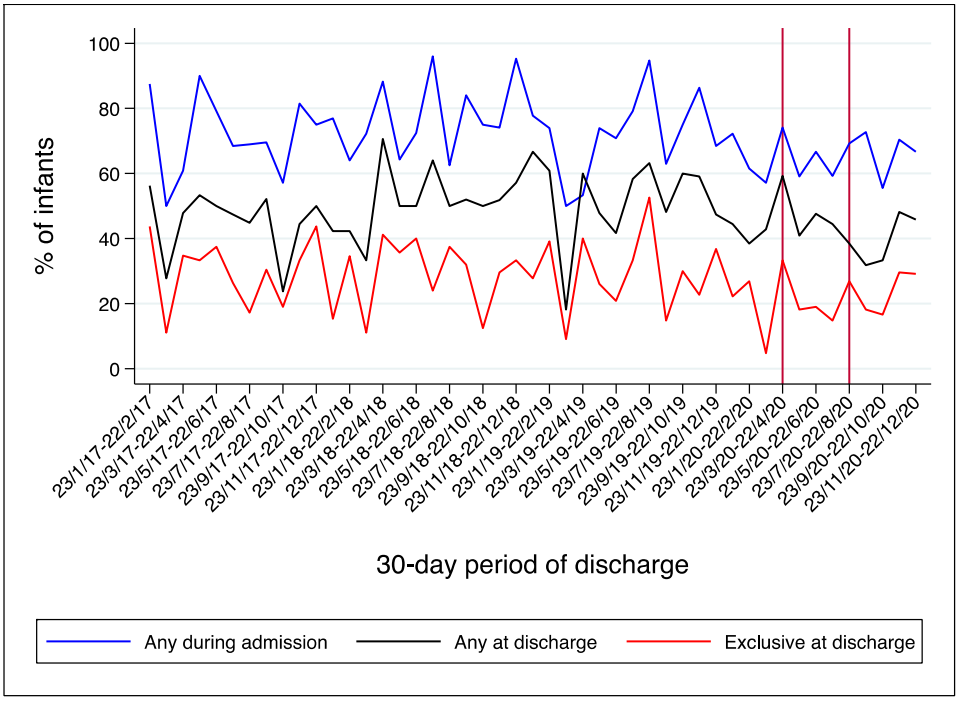
The sensitive analyses were demonstrated in this finding using these two graphs to analyse how sensitive the changes in fluctuations of the breast milk feeding during admission, at discharge and exclusive breast milk feeding at discharge were when i) there were no exclusions based on length of stay as compared to when all infants regardless of length of stay are included, or ii) when instead of using the period of discharge as a criteria of data inclusion, instead of period of admission.




Red vertical lines indicate a period when the restrictions in the neonatal unit were first implemented (period II)

**Figure 3.3: Prevalence of breast milk feeding by 30-days period of admission (no exclusion based on length of stay)**

In comparison to Figure 3.2 which included infants who only stayed more than 24 hours in the neonatal unit, Figure 3.3 which included all infants regardless of length of stay generally shows similar falls in the rate of breast milk feeding at discharge and exclusive breast milk feeding at discharge from the period of 23rd March 2020-August 2020 and all three outcomes in January 2019-April 2019. For any breastmilk feeding during admission, there were a few periods where the breast milk feeding rates were shown to be lower in Figure 3.3 where all infants are included in the analysis.




Red vertical lines indicate a period when the restrictions in the neonatal unit were first implemented (period II)

**Figure 3.4: Prevalence of breast milk feeding based on 30-days period of discharge**

By period of discharge, the prevalence showed no apparent decline as compared to Figure 3.2 on the period of 23rd March 2020-August 2020 but there were consistent falls for all three outcomes in January 2019-April 2019.

### 3.4.3 Regression Analysis

#### 3.4.3.1 Objective 3: What are the odds of breastfeeding during admission and at discharge during COVID-19 pandemic as compared to pre-pandemic period?

In Table 3.8, the adjusted and unadjusted odds ratio for the prevalence of breast milk feeding for all three outcomes were showed for period II, in which the restrictions in the neonatal unit were first implemented, and period III, where restrictions in the neonatal unit were gradually relaxed, relative to the pre-pandemic period (period I).

**Table 3.8: Adjusted and unadjusted odds ratios for the prevalence of breast milk feeding in period II and period III, compared to the pre-pandemic period**

| Period | Any BM during admission | | Any BM at discharge | | Exclusive BM at discharge | |
|---|---|---|---|---|---|---|
| | Unadjusted OR (95% CI, p-value) | Adjusted OR (95% CI, p-value) | Unadjusted OR (95% CI, p-value) | Adjusted OR (95% CI, p-value) | Unadjusted OR (95% CI, p-value) | Adjusted OR (95% CI, p-value) |
| **Period I: Pre-pandemic** | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Period II: 23/3/20-31/7/20** | 0.77(0.49-1.19), p=0.241 | 0.70(0.44-1.12), p=0.140 | 0.95(0.63-1.44), p=0.812 | 0.96(0.62-1.47), p=0.844 | 0.70(0.43-1.15), p=0.157 | 0.71(0.43-1.18), p=0.187 |
| **Period III: 1/8/20-31/12/20** | 0.72 (0.47-1.08), p=0.115 | 0.72(0.46-1.12), p=0.151 | 0.74(0.50-1.09), p=0.131 | 0.71(0.47-1.07), p=0.098 | 0.90(0.58-1.40), p=0.631 | 0.90(0.57-1.41), p=0.632 |

OR; odds ratio, 95% CI; 95% confidence interval. The outcomes were adjusted for GA group, birthweight category, received PN ≥2 weeks, received ventilation ≥3 days, and had any of the conditions that indicate sickness: confirmed NEC, confirmed sepsis, HIE, IVH grade 3/4, and any listed congenital anomalies.

The odds of receiving any breast milk during admission, at discharge and exclusive breast milk feeding at discharge were lower in period II than in the pre-pandemic period, but the differences were not statistically significant in either the unadjusted or adjusted models. In period III, the odds of receiving any breast milk during admission, at discharge and exclusive breast milk feeding at discharge were also lower than in the pre-pandemic period, but again differences were not significant.

There was an approximately 30% reduction in odds for any breast milk feeding during admission and exclusive breast milk feeding at discharge in period II. The magnitude of reduction was similarly shown in period III for any breast milk feeding during admission and breast milk feeding at discharge. There were however smaller

reductions of approximately 5%-10% for breast milk feeding at discharge in period II and for exclusive breast milk feeding at discharge in period III as compared to the pre-pandemic period.

## 3.5 DISCUSSION

For breast milk feeding practices, the term ‘breastfeeding’ that will be discussed in this section is defined as any administration of breast milk (mother’s own milk) by any method of enteral or oral feeding i.e. direct breastfeeding, or alternatives, such as cup, bottle or syringe, or by nasogastric tube. There was no record of the use of donor’s breast milk in this cohort.

The results show that there were differences in characteristics of infants who received breast milk and not received any breast milk during admission and at discharge. Gestational age and birthweight, as well as medical conditions of infants, might have a bigger influence in determining if an infant would receive breast milk in the neonatal unit, in which these factors have been adjusted for in the assessment of odds ratio in Objective 3 in this chapter. There were fluctuations in the breast milk feeding prevalence at discharge during the early COVID-19 pandemic period. There were consistently fewer infants recorded to have breast milk feeding at discharge than those who had any breast milk during admission. There were however natural variations and unexpected fluctuations observed in the prevalence of breastfeeding across the admission periods which make the analysis of the true effects of the COVID-19 pandemic and visitor restrictions in the neonatal unit towards the prevalence of breastfeeding to be challenging. Further discussion follows based on the research questions in this study.

### 3.5.1 Characteristics of Infants Who Received Breast milk during Admission and Exclusive Breast milk at Discharge

Firstly, among infants who received any breast milk during admission, it was shown that they stayed much longer in the neonatal unit than those who did not receive any breast milk during admission. This however complements the other information in this study that infants who received any breast milk were born earlier, had lower birthweight, more of them received ventilation of ≥ 3 days, had received prolonged PN and had more co-morbidities than those who did not receive any breast milk. While this could be demonstrating that being less mature and in a less stable medical condition did not hinder infants from receiving breast milk in the neonatal unit, this could also possibly indicate that these infants had a higher chance of receiving any breast milk feeding due to their long stay when mothers had more time to establish breastfeeding or milk expressing, while the nurses had a longer time to monitor the feeding and possibly encourage mothers to give breast milk.

At discharge, infants who received any breast milk had lower weight and weight Z-score and more of these infants possibly had growth failure as compared to those who did not receive any breast milk. While this is concerning, it should be highlighted that these infants had records of more co-morbidities and so this could be an indirect effect of the sickness rather than nutritional. There was also inadequate information on the feeding practices and nutrition during admission to provide evidence if this has got any correlation with breast milk feeding during admission. From another point of view, this could also indicate that mothers of infants who had more sickness were encouraged to give breast milk rather than formula milk due to its obvious benefits.

On the contrary, those who did not receive any breast milk during admission were recorded to stay for only a median of 5 days, before being discharged to home

(51%) and ward (44%). These infants were also more mature at 36 weeks GA and heavier at birth, had fewer clinical conditions, did not need prolonged PN and fewer of them need ≥ 3 days of ventilation. All these factors had possibly allowed them for earlier discharge at a mean (SD) weight of 2717g. This possibly indicates that because of their short stay in the neonatal unit, these infants might not have had a chance to be given breast milk yet because of mothers' delay in the initiation of breastfeeding or it just did not get to be recorded in the system. This is also supported by the low number of infants from this group who received any breast milk at discharge. However, for more mature infants, 5 days can be considered as a decent length of time, and arguably crucial to begin to try to establish feeding (either direct or expressing) within this period if they were to have any chance of doing so long-term.

Secondly, among those who had exclusive breast milk feeding at discharge, data showed that they were comparatively in a more stable medical condition with fewer clinical diagnoses, no prolonged PN recorded and had comparable but a difference of two days shorter stay in the unit than those who did not receive any breast milk at discharge. This possibly means that these infants could have managed to receive enteral feeding of breast milk earlier as data also showed that 97% of these infants had received any breast milk during admission. This early initiation of breast milk feeding or milk expression has been shown to help sustain the breastfeeding practices for longer until discharge or post-discharge (373).

Yet, similarly as shown in infants who receive any breast milk during admission, there was also a higher proportion of these infants who had a fall of ≥1.28 in changes of weight-for-age Z-score between birth to discharge, indicating possible growth failure. However, again there was no nutritional intake data to analyse if there is any correlation for this to occur in this breastfeeding cohort although studies

did demonstrate that breastfed infants could have slower short-term growth than non-breastfed infants (67,329).

As for those who did not receive any breast milk at discharge, although they stayed in the unit in the comparable duration as those who received exclusive breast milk, they had lower birthweight, a higher number of them were SGA and more of them received ventilation ≥ 3days, had chronic lung disease and prolonged PN. Half of them received any breast milk during admission – which was not extended until discharge, possibly due to the abovementioned factors indicating less stable medical condition which could have caused them to need extra support in terms of both nutrition and medical needs. This is also consistent with studies that showed that infants with morbidities and born at lower GA had a lower likelihood of receiving any breast milk at discharge (113,120) and was regarded as a barrier to breastfeeding from the mothers' perspective (121).

It was also noteworthy to highlight that in both groups of infants who received any breast milk during admission and exclusive breast milk at discharge, the infants' mothers were recorded to be older than those who did not receive breast milk, as also shown in other studies (297). This could be possibly due to older mothers who might have more experience from previous births could have easily initiate breastfeeding earlier and more efficiently (133).

Therefore, for this first objective, it was found that among those who received any breast milk during admission, they stayed significantly longer in the neonatal unit, possibly due to their less stable medical conditions, but this had also given them more opportunity to receive breast milk which was recorded in the system. On the other hand, among those who received exclusive breast milk at discharge, they were found to be more clinically stable which possibly led to them having earlier

oral/enteral feeding with breast milk during admission which was successfully continued until discharge.

### 3.5.2 Breast milk feeding in the neonatal unit during admission and at discharge, before and during the COVID-19 pandemic.

Firstly, there were general fluctuations in the prevalence of breastfeeding observed throughout the whole period of admission included in this study for all three outcomes observed, either for any breastfeeding during admission, at discharge or exclusive breastfeeding at discharge. This is expected, considering the natural variations of the breastfeeding rates in any neonatal units which mostly depended on various factors during the specified admission periods observed such as GA of infants, infants' illnesses, maternal illnesses, maternal preferences and many others. Additionally, the average number of infants admitted to the neonatal unit per month of admission recorded was also small, with a mean (SD) of 22 (4), which could further exacerbate the variation in the breastfeeding rates.

However, during the early COVID-19 period, which is marked in this study starting from 23rd of March 2020 to align with the date when the national lockdown was first implemented and visiting restrictions introduced in the neonatal unit, the prevalence of breastfeeding at discharge were shown to be much lower than other 30-days admission period. This is however with the exception of the unexplained apparent falls in breastfeeding prevalence in the early period of 2019. One of the possible reasons for the sudden fluctuations in the early period of 2019 could be due to data entry error, considering the similar falls in all three outcomes of breastfeeding prevalence, which can be observed even in the sensitivity analyses performed.

In sensitivity analyses, when compared with the prevalence of breastfeeding by 30-days period of admission (no infants exclusion based on length-of stay-basis), the

fluctuations in the breastfeeding prevalence were more obvious in these two periods (early 2019 and early COVID-19 period). This is possibly because of the inclusion of shorter-stay infants which presented a more stable and higher record of breastfeeding due to being older GA or less sick.

However, when compared with the prevalence of breast milk feeding based on 30-days period of discharge (instead of admission periods), the falls during the early 2019 period remain consistent, but the prevalence of all three breastfeeding outcomes during the early COVID-19 period were different – as there were no apparent fluctuations observed. This however makes sense as infants who were discharged home during the early COVID-19 period were delivered and admitted to the neonatal unit before the start of the restrictions due to the COVID-19 pandemic in the UK, so no peculiar changes were observed on the prevalence of breastfeeding for these infants other than what seemingly looks like the natural variations in the breastfeeding rates as other months.

However, in the early COVID-19 period, only the prevalence of breastfeeding at discharge (any breastfeeding and exclusive breastfeeding) were affected, but not breastfeeding during admission. Based on the early COVID-19 visiting policy in the neonatal unit at RDH, mothers (or one of the parents) could only visit once a day (as compared to unrestricted access into the neonatal unit before the pandemic) which means that they may choose to stay all day or for a short period. This indicates that mothers still had a chance to breastfeed their infants as long or as frequently as they could during the stay if they would like to – which possibly explains the unaffected prevalence for any breastfeeding recorded during admission during this period.

Furthermore, in this hospital, the practise of skin-to-skin contact with mothers in the first hour of life was not altered during the pandemic. Even among mothers who

were COVID-19 positive, skin-to-skin care and initiation of breastfeeding in the delivery room were practised with some precautions taken (i.e. mothers had to wear a mask and do proper hand hygiene per WHO recommendations). All mothers were allowed to breastfeed their infants while in the hospital (maternity ward or neonatal unit). This is also supported by studies that have shown that rooming in with the mother and breastfeeding are safe and perinatal transmission of COVID-19 infection to infants from infected mothers are very rarely to happen if close attention to infection prevention and control (IPC) is practised (374).

For breastfeeding at discharge, it is a normal occurrence in an audit setting at the national or international level to observe that initiation of breastfeeding or any breast milk intake to be recorded higher than breast milk intake at later postnatal weeks or discharge or even more elaborate – exclusive breastfeeding at discharge. In the UK, breastfeeding rates have been shown to decrease significantly over the first weeks after birth where from 81% of mothers in the UK initiated breastfeeding, only 34% were still breastfeeding at 6 months (292). Similarly in England alone, figures for 2015/16 show that about 73% of mothers started breastfeeding initially (73.1%), but this also fell to 43.2% at around 6-8 weeks postnatal (293), though these statistics are of the term infants. Specifically, in the neonatal unit, recent data of breast milk feeding at discharge showed that about 60% of eligible babies (<33 weeks non-transferred babies) were still receiving their own mother's milk, either exclusively or with another form of feeding. The rate was recorded to be stable across the years reported since 2015 (253).

Therefore, it is expected that the prevalence of breastfeeding at discharge is lower than the prevalence for any breastfeeding during admission as shown in this study, across all admission periods. However, the apparent fall for breastfeeding at discharge and exclusive breastfeeding at discharge during the early COVID-19

pandemic warrants more explanation. As discussed previously, because the visiting restrictions for one of the parents in the neonatal unit were limited to once a day only, breastfeeding could still be initiated, and this was recorded in the system as “received any breast milk during admission”. However, the overall prevalence for receiving breast milk at discharge and exclusive breast milk was shown to be much lower than receiving any breast milk during admission and the differences between these outcomes were much more evident than in any other admission periods. There are possibly many reasons leading to the drop of breastfeeding at discharge during this period. Firstly, it is obvious that the COVID-19 pandemic has been a cause of significant stress for everyone, including pregnant and newly delivered mothers which could have caused prenatal and postnatal anxiety around the safety of their infants and access to lactation support after birth (375).

Furthermore, with only once a day visiting in the neonatal unit, mothers could have been too tired for frequent breastfeeding even if they stay in the unit all day. In addition, there cannot be swapped with their partners for a lunch break (if mothers want to enter the unit again) and limited access for food to be delivered or brought by family members as in normal situation which could also impact their health especially during the early postpartum period.

These seemingly insignificant factors could add up to cause stress for the mothers and could affect their ability to breastfeed for an extended period until discharge (375). In addition, the use of formula milk could be seen as an easier option as it can be bottle-fed by the nurses when the mothers need to go home, and it does not have to be delivered to the unit and undergo extra screening or precautions due to COVID-19 as is required for expressed breast milk in most neonatal units. This is also further augmented by the situation in early COVID-19 in this neonatal unit where there was a bit of a focus on getting babies to be discharged home as soon

as possible, and probably earlier than it might otherwise happen in normal times. Therefore, this might affect establishing breastfeeding which could take longer than using a formula to bottle feed and switching to formula could also possibly be perceived by parents as an easier option to be discharged home more quickly. Furthermore, following WHO recommendations (264), although breastfeeding and skin-to-skin are encouraged, the mother should take necessary precautions such as wearing a mask, practice good hand hygiene, and avoid coughing onto her chest or even consider washing her breast with soap and water prior to each feeding. However, all these precautions although very important could be very uncomfortable and inconvenient for the mothers especially those who want to direct breastfeed their infants. The same applies to when mothers are expressing their milk. The extra efforts in regard to these hygiene precautions that are needed to be done before pumping their milk for every 2-3 hours could have made them feel too tired or demotivated.

In addition, other effects of the COVID-19 pandemic, other than visiting restrictions and the consequences especially to the mothers, unexpected factors such as home quarantine or self-isolation due to confirmed or suspected COVID-19, hospitalisation due to complications of COVID-19, and fear of the COVID-19 transmission during travel to the hospital or being in the hospital might also pose additional challenges and stress among mothers. These could also impair the extended breastfeeding rates among admitted infants especially those who had to stay longer in the neonatal unit (376). Furthermore, for mothers with suspected or confirmed COVID-19, separation from their infants due to the need for self-isolation for 7-10 days is a long pause for breastfeeding which may lead to total discontinuation for the breastfeeding altogether. During isolation, expressing breast milk, although permissible, might induce feeling of anxiety and worries that they

could infect their already vulnerable infants with their EBM, especially when lack of support is provided.

Other than that, there is no alternative feeding options for infants whose mothers were unable to breastfeed them due to COVID-19 in any published guidelines other than the use of formula milk. Support in the use of expressed breast milk when mothers were unable to directly breastfeed or the use of donor breast milk should be highlighted as a safe and recommended feeding option in the neonatal unit during pandemics (366). It should be emphasised that as serious illness due to COVID-19 appears rare in infants (349), it may be that some hospital policies intended to be cautious against COVID-19 transmission incidentally pose a greater risk of harm to the infants considering that breastfeeding which is known to provide protection towards neonatal infections such as NEC and sepsis is possibly overlooked.

### 3.5.3 The prevalence of breast milk feeding in period II and period III, compared to the pre-pandemic period (period I)

In this study, period II was marked beginning from 23rd March 2020 until 31st July 2020 which was on the early COVID-19 pandemic when restrictions in the neonatal unit were first implemented while in period III starting from 1st August 2020 onwards, restrictions in the unit were gradually relaxed.

It was observed that there were generally reductions in odds for all three breastfeeding outcomes in period II and period III as compared to the pre-pandemic period, but the differences were not statistically significant in either the unadjusted or adjusted models. This could be due to the small sample size in this study which may not be sufficiently powered to detect a difference between the periods.

In addition, as discussed earlier, the visiting policy during the early COVID-19 pandemic in the unit still allows unlimited hours of stay for mothers even it is only once a day and breastfeeding were encouraged as in normal circumstances. These important factors might contribute to the non-significant reduction in overall breastfeeding prevalence during the pandemic as compared to the pre-pandemic period.

In a study that explored parental perceptions of the impact of restricted visiting policies to neonatal intensive care units (NICU) during the COVID-19 pandemic from May-August 2020 (362), responses received from parents and families of infants hospitalised in the participating six tertiary NICU (four from the UK and two from the USA) showed that visitation limited to a single visitor with no restrictions on duration was the most frequently reported policy; 63% (140/217) and mild to severe impact on breastfeeding was reported by 36% (75/209) of the respondents. Looking at specifically the responses from UK's respondents, the centre with the most rigid restrictions in May and June 2020 reported higher rates of insufficient bonding, being unable to be more involved in their infants' care and more mild and severe adverse impacts on breastfeeding due to the restrictions. As for the centre with the least restrictive visiting policy, the lowest rates of inability to participate in infants' care and insufficient bonding were reported.

Additionally, a Turkish study that studied the effects of the COVID-19 pandemic on the delivery of expressed breast milk to the neonatal unit (376) found that an informed guideline on the breastfeeding option and adequate support and education offered for the mothers during the later phase of the pandemic allowed the infants to have extended breastfeeding even after discharge home. This is despite the lower rate of expressed breast milk feeding delivery to the unit during the early COVID-19

pandemic as compared to the pre-pandemic period due to lack of proper feeding guidelines in the beginning.

Therefore, in this study, in comparison between the two periods (period II and period III), we would hypothesise that the odds for receiving any breast milk during admission or at discharge should be higher in period III than in period II considering that the restrictions during the later period have been eased and mothers should have fewer difficulties in accessing the unit and continue breastfeeding. However, results showed that the magnitude of reduction of odds of receiving any breast milk during admission was similar for both periods as compared to pre-pandemic, while for breastfeeding at discharge, period III showed a higher reduction in odds for receiving any breastfeeding at discharge and period II showed higher reduction in odds for exclusive breastfeeding at discharge.

Hence, it is important to analyse the difference between these two breastfeeding outcomes at discharge: as “receiving any breast milk at discharge” would mean that infants could still receive a higher amount of formula milk but only some breast milk at discharge which if there is any reduction in breastfeeding during the whole stay because of the restrictions, it would be hardly distinguished due to this broad definition of outcome.

On the other hand, for the outcome “received exclusive breast milk feeding at discharge”, this would mean that the analysis only included infants who only had breast milk at discharge, with no mixture of formula milk – which possibly indicates that infants have been receiving a lot of breast milk during admission (probably more than formula milk, if any) to be able to have only breast milk feeding recorded at discharge. Theoretically, this outcome would be the better indicator of changes to the breastfeeding prevalence, although it might be limited by the smaller number of

infants discharged with this criterion (exclusive breastfeeding: n=296 (27.6%) vs any breastfeeding at discharge: n=513 (47.9%)).

Therefore, if looking at the outcome based on infants who received exclusive breastfeeding at discharge, it was observed that the reduction of odds in exclusive breastfeeding at discharge was much smaller in period III, about 10% – when the mothers have unrestricted access to the unit as compared to period II when there was about 30% reduction in odds for exclusive breastfeeding during the restricted access to the unit for mothers/parents.

This is important as for a longer period of breastfeeding or exclusive breastfeeding to be a success, mothers need to put more effort into breastfeeding in terms of direct breastfeeding or milk expression. When there was restricted access to infants, it is common to hypothesise that these mothers might have difficulty having longer time for skin-to-skin with their infants, more bonding time with their infants, more frequent breastfeeding, and for milk expression, as discussed earlier, they might need to take extra precautions in handling breast milk, more than what they usually do in a normal situation.

Therefore, in the challenging environment in the neonatal units to care for sick/premature infants, on top of the anxiety around the safety of their infants with COVID-19, all of these stress factors can negatively affect lactogenesis (135) and leads to reductions in the maternal breast milk supply (136). This undoubtedly could have affected the ability of mothers to continue breastfeeding for a longer period or exclusively breastfeed their infants until discharge.

## 3.6 CONCLUSION

Neonatal units present a distinctive setting where sick or preterm infants often need to stay for a longer time and parents plays a vital role as part of their care and are

no longer considered as visitors in the unit. However, during the COVID-19 pandemic, a lot of policy changes have been implemented in the neonatal unit mainly to prevent transmission to the patients as well as healthcare staff that disrupted the parental presence and their ability to bond and care for their infants as in normal circumstances. This is speculated to affect the successful initiation and continuation of breastfeeding as the ongoing contact between mothers and infants is very essential for the matter and could have an important impact on short and long-term outcomes for both mothers and infants, including mortality, health, and development outcomes (62).

Therefore, in this study, as we hypothesised that this pandemic and its consequences on the change of neonatal unit policy might indirectly reduce the breastfeeding prevalence in the neonatal unit, although some general reduction in breastfeeding prevalence was observed, it was not significant. This is possibly due to the natural variations of breastfeeding rates in the neonatal unit that usually depends on the general conditions of the infants as well as the small sample size recorded especially for the exclusively breastfeeding practice as also demonstrated at a national level.

However, the most important factors could also be attributed to the unaltered breastfeeding policy in the study unit in which as recommended by the WHO, breastfeeding is encouraged immediately after birth, there was no mother-infant separation in place and the practice of skin-to-skin contact remains unaffected in this study unit. In addition, although the visiting policy in the early COVID-19 pandemic only allowed one of the parents to care for the infant once a day, it was providentially for unlimited hours, and this could have also helped in minimising the impact of breastfeeding fluctuations rather than more restrictive visiting policy in some other neonatal units or in another country.

The findings however highlight the complex challenges in implementing guidelines in the neonatal unit during a rapidly changing environment where with the limited evidence available, quick decisions need to be made that must give greater benefits to not only for the infants' well-being but also the whole organisation that involves in the care of these infants. Some expected compromises on the established standard of care such as breastfeeding policies should also be considered and be minimised as much as possible. Frequent evaluation on the policy with the availability of emerging evidence where possible should be made to ensure that any changes are relevant and not causing a long-term adverse effect to the infants in general.

## 3.7 STRENGTHS AND LIMITATIONS

To my knowledge, this is the first study in the UK to date that presents data on the impact of COVID-19 visiting policy and other restrictions on breastfeeding prevalence in the neonatal unit. This study presents complete infants' demographic and breastfeeding data extracted from the BadgerNet database from the period of admission from 2017-2020. In addition, three outcomes of breastfeeding were showed in this study to determine if impacts of the COVID-19 pandemic can be observed differently between the prevalence of breastfeeding during admission and at discharge. Additionally, the different periods of COVID-19 pandemic were also distinguished in the study to better characterise the impact of the neonatal unit's policy changes. This was to show the differences when guidelines and evidence on infants' care during a pandemic are still lacking in the early phase, versus the second phase of the pandemic when more emerging evidence especially on COVID-19 transmission and appropriate policy that should be implemented were suggested.

However, there were also limitations recognised in this study. Firstly, due to the small sample size of infants included and common variations in breastfeeding rates observed across the admission periods, more rigorous methods of trend analysis such as interrupted time-series analysis could not be undertaken to better demonstrate the impact of COVID-19 on breastfeeding prevalence. This is further exacerbated by a few unexpected and unknown fluctuations in the breastfeeding prevalence that could have been data entry error but makes the analysis of the true effects of COVID-19 challenging. Secondly, although complete maternal and infants' demographic data are available in the database, I could not include all possible confounding factors that might affect breastfeeding when adjusted for the regression analyses comparing breastfeeding prevalence in pre-pandemic and during pandemic due to the small sample size of infants included in the study. However, important factors that might be more likely to impact breastfeeding have been included which are GA group; birthweight category; sex; IMD quantile; and the binary variable indicating overall sickness which includes days on parenteral nutrition and ventilation, congenital anomalies and other important diagnoses such as NEC.

Lastly, as in many database studies involving manual data entry into the system, this study is also prone to missing information, inconsistent data or duplicate information entered in certain variables, which I have to clean and exclude to ensure that the final sample of infants included in this study consist only infants with no ambiguous information. Because of this, some useful variables that can be presented such as "mothers' intention to breastfeed" cannot be extracted due to a lot of missing or incomplete data entered. In addition, there is also missing data on the use of breast milk (although minor), and some doubts raised if the recording of breast milk data is precise. This is due to the nature of information recording in

BadgerNet that lacks a guideline in identifying what some of the indicators used are for easy reference.

Nevertheless, this study provides well-demonstrated data on the prevalence of breastfeeding during admission in the neonatal unit and at discharge from 2017-2020 in which the impact of the COVID-19 pandemic can be generally provided for early assessment. Future studies are suggested to include more infants possibly from many neonatal units with different parental visitation and breastfeeding policies to further demonstrate if there is a significant impact of COVID-19 on the prevalence of breastfeeding in the neonatal unit. Further recommendations for future studies will be discussed in the final chapter.

In neonatal units, other than prioritising efficient feeding practices such as the use of breast milk for preterm and sick infants, identifying other factors that may affect infants' conditions and consequently the establishment of feeding and growth outcomes is also very important. In this regard, the next chapter will explore the diagnosis of gastro-oesophageal reflux disease (GORD) and the use of anti-reflux medications among preterm infants in neonatal units in England and Wales.

# CHAPTER 4: GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AND ANTI-REFLUX MEDICATION USE AMONG PRETERM INFANTS IN NEONATAL UNITS IN ENGLAND AND WALES

## 4.1 INTRODUCTION

Gastro-oesophageal reflux (GOR), defined as the physiologic passage of gastric contents into the oesophagus can be a physiologic condition among preterm infants (377). It usually occurs due to the reasonably abundant volumes of milk/liquid intake as well as the supine position of feeding which leads to the easy passage of liquid content into the oesophagus (187). GOR is often diagnosed in practice based on clinical and behavioural signs such as feeding intolerance, poor growth, apnoea, desaturation and bradycardia, worsening pulmonary disease, and other nonspecific behavioural signs (241). However, physiologic GOR can worsen and lead to gastro-oesophageal reflux disease (GORD) when the reflux of gastric contents into the oesophagus causes problematic symptoms that affect daily functioning or cause complications such as oesophagitis or stricture (171,172).

In neonatal units, the management of GORD and stress ulcers are one of the main reasons for the prescription of anti-reflux medications, specifically Histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPI). As with many medications used among neonates, these medications are currently unlicensed to use in the UK and many other countries for patients below 3 years old (oral medications) and below 6 months old (injections) (231), though *off-label* use is frequently reported (378). Moreover, there have also been mixed reports from studies on the effectiveness of these medications in treating reflux-related

symptoms (379) as well as the adverse effects reported in cohort and case-control studies (203).

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and European Society for Paediatric Gastroenterology Hepatology and Nutrition (NASPGHAN and ESPGHAN combined) clinical practice guidelines (171) suggests non-pharmacological approaches to GORD before pharmacological therapy. Similarly, the American Academy of Paediatrics recommends that anti-reflux medications should be used with caution, if at all, in preterm infants due to lack of evidence of efficacy and possible significant harm (197).

In the UK, two survey studies of neonatal health care professionals, in 2004 (241) and 2018 (242), revealed that clinicians reported frequently prescribing anti-reflux medications in neonatal units. Dhillon and Ewer (241) reported that, in 2004, nearly all respondents used anti-reflux medications to manage GOR. In 2018, another survey showed that the use of anti-reflux medications remained popular (242) despite the increasing evidence of lack of efficacy and possible harm. Both studies, analysed the use of medications as reported by clinicians. There are no studies that have analysed the prevalence of GORD diagnosis and the actual use of anti-reflux medications in neonatal units in the UK.

Therefore, for this study, we used the National Neonatal Research Database (NNRD) to conduct a retrospective cohort study to describe patterns of GORD diagnosis and use of anti-reflux medications among preterm infants in England and Wales. The findings from this study are expected to contribute to the knowledge of current GORD diagnosis among preterm infants in neonatal units in England and Wales as well as patterns of use of anti-reflux medications.

## 4.2 STUDY OBJECTIVES

1. To describe the prevalence of the diagnosis of GORD in preterm infants and characteristics of infants with and without GORD
2. To report on the proportion and characteristics of infants with prescriptions for anti-reflux medications and feed thickener
3. To describe the agreement between GORD diagnosis and use of anti-reflux medications, and the prevalence and change over time of GORD diagnosis and use of anti-reflux medication
4. To describe the different types of anti-reflux medications prescribed in neonatal units and trends in their use over time

## 4.3 METHODOLOGY

### 4.3.1 Study design

Retrospective cohort study using operational National Health Service (NHS) data from the National Neonatal Research Database (NNRD) for the period of 2010 until 2017.

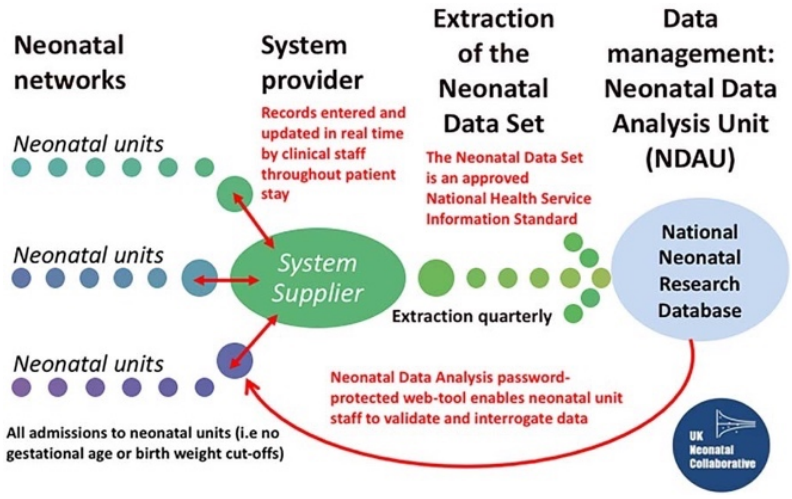
#### 4.3.1.1 Introduction to the UK National Neonatal Research Database (NNRD)

The National Neonatal Research Database is a repository of clinical data of all admissions to National Health Service (NHS) neonatal units in England, Wales and Scotland. A total of 200 neonatal units in England, Scotland and Wales known as the UK Neonatal Collaborative have contributed their data to this database. It is fully managed by the Neonatal Data Analysis Unit (NDAU) which was established in 2007 at the Chelsea and Westminster Hospital campus of Imperial College London (370). This independent academic unit has received approval from National

Research Ethics Committee (10/80803/151) and the Caldicott Guardians of NHS trusts to build NNRD by using the anonymised patient-level data.

Standardised electronic patient data entered by clinicians and nursing staff into BadgerNet (Clevermed Ltd) are stored on a secure NHS server in individual neonatal units. These predefined data are extracted and transmitted quarterly to the Neonatal Data Analysis Unit to form NNRD. This secure transfer of data removes any personal or identifiable information (i.e. NHS numbers/names). Records of a patient over any episodes of care across different hospitals are linked and merged by using a unique identifier - the BadgerID (created by Clevermed Ltd), cleaned for missing values and finally entered into the NNRD as a single record per patient (Figure 4.1).

The NNRD is available for activities such as health services evaluations, quality improvement projects and also for observational and interventional research. To date, NNRD comprises data for approximately one million babies and 10 million days of care (282).




Flow chart indicating the process of establishing data for NNRD from neonatal units. Figure from (370).

**Figure 4.1: Flow chart of NNRD data management**

#### 4.3.1.2 Data structure of NNRD

The NNRD contains data on approximately 430 data items in The Neonatal Dataset (NDS) (380) approved in 2013 as a national NHS Information Standard by the NHS Information Standards Board (now NHS Digital) coded as ISB1595 version 1.0, now Standardisation Committee for Care Information (SCCI) 1595 (381) which can be categorised into:

i. “once only” or static basic demographic details per infant such as sex, gender, month and year of birth, birth weight, and gestational age

ii. episodic data that are taken once per admission/hospital stay such as admission time, admission diagnosis, clinical outcomes, co-morbidities. An infant may have several episodes of care if they are transferred between different neonatal units as part of their care

iii. daily data that includes all daily care information recorded on a daily basis during an admission such as feeding, medications, respiratory support, and surgical procedures

iv. ad-hoc or “only if” data items that are only available for some infants such as retinopathy of prematurity (ROP) screening, cranial ultrasound scan and two-year neonatal assessment outcomes records.

Each data item entered is compatible with national and international standard nomenclature such as *International Classification of Diseases* codes (ICD10) and mapping to Systematised Nomenclature of Medicine–Clinical Terms (SNOMED-CT).

#### 4.3.1.3 Database validation and completeness

A validation study which compared NNRD population coverage in 2008-2014 with data on live births in England from the Office for National Statistics (382) showed that the NNRD contains data on 100% of infants born alive from 25 to $31^{+6}$ weeks' GA from 2012 until 2014, 90% of infants born at 24 weeks and 70% of infants born at 23 weeks. There was a decrease in the percentage of infants with an NNRD record for more mature preterm infants: 98% for infants 32 to 33 weeks GA, 90% for 34 weeks GA, 60% for 35 weeks GA and 40% for 36 weeks GA. However, the trend over time shows an increasing percentage of these moderate-to-late preterm infants (> 32 weeks GA) with an NNRD record.

This validation study also compared the completeness of patient characteristics and intervention data between NNRD and the multi-centre randomised controlled trial, Probiotics in Preterm Study (PiPS) (383). The PiPS study used conventional paper Clinical Record Forms (CRF), that were subjected to high quality data checks before entering onto The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP) standards trial database. From the evaluation, the completeness of data on patient characteristics in the NNRD was found to be generally higher with the exception of five characteristics (>4% missing): Estimated date of delivery (EDD), maternal ethnicity; maternal Lower-Level Super Output Area (LSOA); five-minute Apgar score; and mode of delivery.

However, for processes/interventions variables, major discordancy (≥2days difference) were found between these two databases for some complex variables involving durations or counting days, such as the type of feed given on the first day of feeding (22.3% disagreement, 95% CI 19.6–25.1%) and the summary of different

milks received for the first 14 days (13.8% disagreement, 95% CI 12.0–15.8%), though high agreement was found for day of first milk feed, with only 2.8% major discordancy (≥2 day difference). This was however deemed reasonable as NNRD data derived information based on the raw daily care data set, and 100% accuracy of such detailed information should not be expected given the different structure of these two databases. Additionally, for comparison of outcome variables, the sensitivity of NNRD data for identifying infants' survival to discharge was 100%, for adverse outcomes was 50–87%, and the specificity was over 85% for all outcomes.

This validation shows that the NNRD is a rich resource of routinely collected neonatal data which can provide complete, high population coverage and reliable quality data for research purposes.

### 4.3.2 Ethical approval

For this retrospective cohort study, ethical approvals were obtained from the Yorkshire & The Humber – Leeds East Research Ethics Committee and Health and Care Research Wales (HCRW) (REC reference: 18/YH/0209) and The National Neonatal Research Database -REC Number 16/LO/1093, as part of the NDAU Data Extraction Request Form (dated 06/12/2017) and the COMMON study – [Protocol Version 1.0 date 26/03/2018].

### 4.3.3 Study participants

#### 4.3.3.1 Identification of study cohort

The initial dataset contained data on all infants with GA of 20 to 45 weeks admitted from 2009 to 2018. A set of inclusion and exclusion criteria as listed below were applied to derive the final dataset.

#### 4.3.3.2 Inclusion criteria

- Preterm infants born at 23 to 36 completed weeks gestational age
- Admission into neonatal units from 2010 until 2017

#### 4.3.3.3 Exclusion criteria

- Missing data on sex, birthweight, month/year of birth
- Missing data for 1 or more days or episodes of care
- Late admission into neonatal unit: >24 hours for infants <34 weeks GA and > 7 days for infants 34-36 weeks GA
- Infants with extreme birth weight for gestational age Z-score of greater than -4SD or +4SD

### 4.3.4 Data Extraction Procedure

#### 4.3.4.1 Data extraction for demographic variables and basic characteristics of infants' care

Table 4.1 shows the demographic variables which were extracted or derived from the raw NNRD data files requested (Appendix 8). These were used to build a study dataset containing information for all eligible infants.

In a small number of cases there were contradictory data for GA, sex, month/year of birth, month/year of admission and birthweight recorded for different episodes of care for the same baby. In this instance, values were extracted from the first row of data (i.e. a baby's first episode of care). Where there were no values or "999" values recorded across all of an infant's episodes of care these variables were considered missing.

Next, the STATA command “zanthro” (384) was used to generate a birthweight for gestational age Z-score with reference to the UK-WHO Preterm Growth Reference. Infants with an extreme Z-score, defined as more than +4 SD or less than -4 SD, were flagged for exclusion due to possible data entry errors.

From daily care data, day of life at first day of admission was generated from a variable called “daydateanon” which indicates the number of minutes after birth (1440 minutes = 24 hours). Therefore, from this definition, day of life at first day of admission was set as day 1 if “daydateanon” was equal to, or less than 1440 on the first day of admission. If “daydateanon” for the first day of admission was greater than 1440 but less than or equal to 2880, this was classified as the second day of life, and so on. A variable indicating day of life for each subsequent day in the daily care data was then generated. Having calculated day of life for each day of care, the “current” postmenstrual age (PMA) (in completed weeks) was then calculated for each day of care by combining GA at birth, age at admission and the day of care.

This “current PMA” variable serves as the point of data extraction when looking at PMA for first diagnosis of GORD or prescriptions of medications. Additionally, from the daily care data, infants with missing days of care were also identified by using “daydateanon”, defined as: i) differences of >1440 (more than 24 hours or 1 day) between subsequent recorded days of data or ii) no daily data recorded at all. This was then merged with the “missing episodes” variable generated from the episodes data that indicates inconsistency between the episode number of the last episode and the total number of episodes for an individual infant.

Finally, we identified infants who were admitted late into neonatal care. In usual clinical practice, infants born less than 34 weeks GA are admitted straight from the delivery room to neonatal care, whereas infants born from 34 weeks onwards might be admitted after a short stay on the postnatal ward for observation. We therefore counted as a late admission in infants <34 weeks whose first daily record was created >1440 minutes after birth, and infants 34-36 weeks whose first daily record was created >10080 minutes (i.e. 7 days) after birth. Infants who were in this category were excluded to avoid possible inaccuracy in data analysis due to missing or inaccurate data.

**Table 4.1: Data extracted for demographic information of the infants**

| Variable | Data extraction and categorisation |
|---|---|
| Sex | Male; female; missing |
| Birthweight | In grams, and categorised as follows:<br>• Birthweight category : Extremely low birth weight (ELBW, <1000g), very low birth weight (VLBW,<1500g), low birth weight (LBW,<2500), normal birth weight (NBW, ≥2500g)<br>• Extremely low birthweight (ELBW, <1000g)<br>• Birthweight less than 1500g<br>• Weight for GA Z-score at birth<br>• <-2 SD weight Z-score at birth<br>• Extreme Z-score (> +4 SD or < -4 SD) |
| GA (at birth) | In completed weeks, categorised as follows:<br>• <28 weeks (extremely preterm infants), 28-31 weeks (very preterm infants) and 32-36 weeks (moderate to late preterm infants)<br>• PMA at discharge/died<br>• GA less than 28 weeks<br>• PMA at each drugs' first usage and first GORD diagnosis |
| Total episodes of care | Continuous; number of missing episodes |
| Month and year of birth | Combination of month/year of birth |
| Month and year of admission | Combination of month/year of admission |
| Final discharge destination | Categorised as follows:<br>• Home; transfer for further medical care; died before discharge; missing. |
| Total days of care | Generated these variables:<br>• Missing days of care<br>• Late admission :<br>-In infants <34 weeks (first daily record was created >1440 minutes after birth)<br>-Infants 34-36 weeks (first daily record was created >10080 minutes (i.e. 7 days) after birth<br>• Early neonatal death (died in the first 7 days of life) and late neonatal death (died after 7 completed days of life to 28 days of life) |

#### 4.3.4.2 Data extraction for drugs variables

Using the daily care database, indicator variables were created for each day of care to show whether an infant was prescribed each of the following drugs on that day, based on the list of anti-reflux medications for all the drug formulations for GORD

available in the UK according to the British National Formulary (BNF) (223). Since there are some inaccuracies and inconsistencies in the “drugsday” variable on how the prescribed drugs are recorded in terms of spelling and brand names, different possible entries were included Table 4.2 to ensure that instances of prescribing were identified for analysis.

**Table 4.2: Data extracted for infants' medications use**

| Medication group | Individual drug | Entries within NNRD data |
|---|---|---|
| H2RA | Ranitidine | “ranitidine” |
| PPI | Omeprazole and Lansoprazole | “omeprazole", "lansoprazole", "lanzoprazole", "lonsorprazole", |
| Gaviscon | Gaviscon | “gaviscon” |
| Prokinetic agents | Domperidone, Metoclopramide, Erythromycin | “domperidone”, "metoclopramide", "erythromycin","erthromycin" |
| Feed thickener | Instant Carobel, Nutilis, Thixo-D, Vitaquick, Thick and easy | carobel", "carobal", "nutilis", "thixo-d", "vitaquick", and "thick and easy” |

For each infant, a variable was then created to show whether they were prescribed each drug at least once during their stay, as well as PMA, day of life and day of admission at first prescription, prescriptions received at on the last day of admission (taken as a proxy for being discharged on a particular medication) as well as number of days of prescription.

#### 4.3.4.3 Data extraction for diagnoses variables

For information on diagnosis of GORD, the same pattern of commands was used as in extracting the medications from the daily care data, searching the “principal diagnosis at admission”, “daily diagnoses” and “diagnoses at discharge” fields in the

NNRD. Entries within NNRD data that were searched for were: “gastro-oesophageal reflux disease", "gastro-oesophageal reflux", "reflux - gastro-oesophageal" and “reflux oesophagitis".

Infants who had any record of GORD, either from episode admission data, episode discharge data, or daily diagnoses, were considered to have had a diagnosis of GORD. In addition, additional variables were also generated to extract PMA at first diagnosis, day of life and day of admission at first diagnosis.

### 4.3.5 Data analysis

Statistical analysis was performed using STATA 16.0 software (Stata Corp. College Station, TX). Descriptive statistics were used to describe the demographic characteristics of infants according to gestational age group. Values were presented as numbers and percentages for categorical data and for continuous variables, mean (± standard deviation, SD) was used for normally distributed data and median (inter-quartile range, minimum and maximum values) for non-normally distributed data. The Student-t test was used to compare normally distributed continuous variables between gestational age groups and the Mann-Whitney test for non-normally distributed variables.

Given the large number of statistical comparisons, here and throughout this chapter p-values are presented to 3 decimal places, and confidence intervals are given where appropriate, to enable the reader to judge the full weight of evidence.

Specific methods used to address the four study objectives are described below:

**Objective 1: To describe the prevalence of the diagnosis of GORD in preterm infants and characteristics of infants with and without GORD**

For this objective, diagnosis of GORD from different sources in the database were retrieved and the prevalence was calculated according to the gestational age (GA) group. Three different sources of information indicating a GORD diagnosis were considered: 1) Diagnosis at admission 2) Diagnosis at discharge 3) Daily care data

Next, the PMA, day of life and day of stay at the first diagnosis of GORD were extracted from daily care records based on GA group. Characteristics of infants with and without diagnosis of GORD were also compared.

Logistic regression was then used to calculate odds ratios (ORs) for associations between infants' characteristics and the diagnosis of GORD. Adjusted ORs were calculated adjusting for the following confounders specified *a priori*: GA less than 28 weeks; birthweight less than 1500g; female; and birthweight Z-score < -2SD.

**Objective 2: To report on the proportion and characteristics of infants with prescriptions for anti-reflux medications and feed thickener**

For this objective, records of prescribing of anti-reflux medications and feed thickeners during admission and at discharge were retrieved from the database. The prevalence of any use of a) anti-reflux medication and b) feed thickener was calculated, overall and by GA group. Next, descriptive statistics (median, range and IQR) related to prescription practices were extracted for all infants and each GA group individuals: PMA at first prescription; day of life at first prescription; and number of days of prescriptions. Characteristics of infants with and without prescriptions of anti-reflux medications and feed thickener were also compared.

Logistic regression was also used to calculate odds ratios (ORs) for associations between infants' characteristics and the prescription of anti-reflux medications and feed thickener during admission. Adjusted ORs were calculated adjusting for the following confounders specified *a priori*: GA less than 28 weeks; birthweight less than 1500g; female and birthweight Z-score < -2SD.

**Objective 3: To describe the agreement between GORD diagnosis and anti-reflux medications' use and prevalence of GORD diagnosis and prescription of anti-reflux medications' use over time**

For this objective, the agreement between the diagnosis of GORD and prescription of anti-reflux medications and feed thickener were analysed and number of days of use were also extracted for comparison. A Venn diagram which illustrated the relation between GORD diagnosis, anti-reflux medications use and feed thickener use was also presented.

Next, prevalence of GORD diagnosis, anti-reflux medication and feed thickener use during admission were also extracted for each year of admission from 2010 to 2017, as well as by GA group.

**Objective 4: To describe the types of anti-reflux medications prescriptions in neonatal units and trends of different anti-reflux medications' use over time**

For this final objective, pattern of medication prescription by GA group were derived from the dataset, specifically which medications were most commonly used and were given first, types of medications used, and most common combination of medications used. Trends in prescribing of different anti-reflux medications were analysed from 2010-2017 and shown in a graph.

## 4.4 RESULTS

In this section, the population baseline data are presented first, which includes overall infant characteristics at birth and during admission, until discharge (or death where infants died before discharge). This is followed by the main results which are presented according to the four objectives that are stated earlier.

### 4.4.1 Characteristics of the study population

Figure 4.2 below shows the flow chart of the included infants in the completed database analysis, which is based on the data received from NDAU. These infants were then excluded based on the exclusion criteria of the study, which then leads to the final number of 251,644 infants with complete data for analysis.

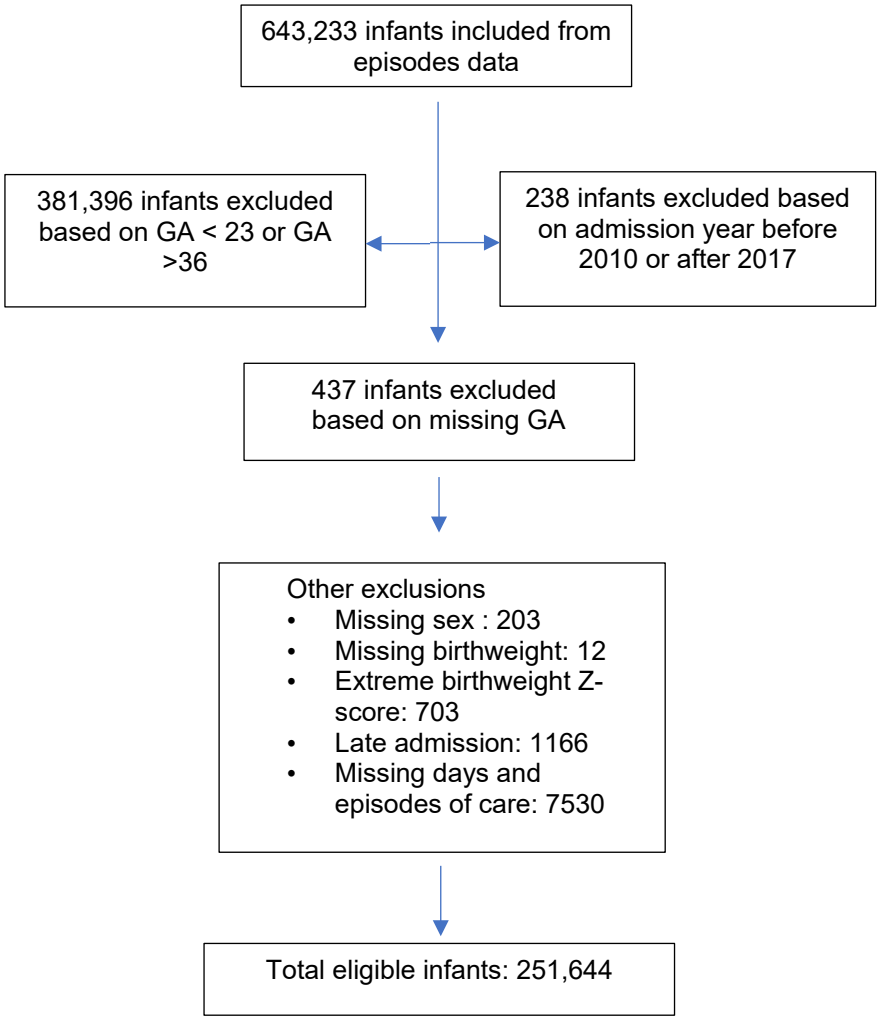



**Figure 4.2: Flow chart of the inclusion of eligible infants**

Table 4.3 shows characteristics of the study participants based on the three main category of gestational age (GA) group.

**Table 4.3: Basic characteristics of infants**

| Outcome, n(%) | All infants n=251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n=193,536 |
|---|---|---|---|---|
| **Total infants** | 251,644 | 17,501(7.0) | 40,607(16.1) | 193,536(76.9) |
| **Female** | 115,087(45.7) | 8,077(46.2) | 18,519(45.6) | 88,491(45.7) |
| **Gestational age (GA) (weeks)±** | 34(32-35, 23-26) | 26(24-27, 23-27) | 30(29-31, 28-31) | 35(33-36, 32-36) |
| **Birthweight (g)+** | 2,030(663) | 830(194) | 1,379(315) | 2,275(518) |
| **Birthweight Z-score+** | -0.08(1.06) | -0.13(0.87) | -0.02(1.01) | -0.08(1.09) |
| **Birthweight Z score<-2 SD+** | 9,375(3.7) | 520(3.0) | 1,435(3.5) | 7,420(3.8) |
| **Birthweight category** | | | | |
| **Extremely low birthweight, (<1000g)** | 18,612(7.4) | 13,797(78.8) | 4,555(11.2) | 260(0.1) |
| **Very low birthweight, (<1500g)** | 34,349(13.6) | 3,695(21.1) | 21,498(52.9) | 9,156(4.7) |
| **Low birthweight, (<2500g)** | 138,610(55.1) | 9(0.1) | 14,518(35.8) | 124,083(64.1) |
| **Normal birthweight, (>2500g)** | 60,073(23.9) | 0 | 36(0.1) | 60,037(31.0) |
| **Total episodes of care±** | 1(1-1,1-13) | 2(1-3,1-13) | 1(1-2,1-11) | 1(1-1,1-9) |
| **Length of hospital stay (day)±** | 14(6-28, 1-527) | 83(58-107, 1-527) | 43(33-57, 1-353) | 11(5-18, 11-272) |
| **PMA at discharge (weeks)±** | 36(35-36, 23-85) | 38(37-41, 23-85) | 36(35-37, 28-81) | 36(35-36, 32-71) |
| **Day of life at discharge (day)±** | 14(7-28, 1-428) | 92(76-113, 1-428) | 44(34-57, 1-353) | 11(5-18, 1-272) |
| **Day of stay at discharge (day)±** | 14(6-28, 1-428) | 92(76-113, 1-428) | 44(34-57, 1-353) | 11(5-18, 1-272) |
| **Discharge destination** | | | | |
| Home/social care | 200,765(79.8) | 12,365(70.7) | 38,025(93.6) | 150,375(77.7) |
| Transfer (further care) | 43,628(17.3) | 937(5.4) | 1,169(2.9) | 41,522(21.5) |
| Died | 6,598(2.6) | 4,072(23.4) | 1,309(3.2) | 1,217(0.6) |
| Missing | 653(0.3) | 127(0.7) | 104(0.3) | 422(0.2) |
| **Time of death*** | | | | |
| Early neonatal death (1-7 days of life) | 3,565(54.0) | 2,028(49.8) | 748(57.1) | 789(64.8) |
| Late neonatal death (8-28 days of life) | 1,778(26.9) | 1,176(28.9) | 326(24.9) | 276(22.7) |
| Died after 28 days of life | 1,255 (19.0) | 868(21.3) | 235(18.0) | 152(12.5) |
| **PMA at death (weeks)±** | 28(25-33, 23-101) | 26(24-28, 23-101) | 30(29-32, 28-66) | 35(33-36, 32-66) |
| **Day of life at death (day)±** | 6(2-20, 1-527) | 8(2-24, 1-527) | 5(2-18, 1-261) | 4(2-11, 1-231) |

± Median (IQR, range), + Mean (SD), PMA, postmenstrual age

*Percentages are from total number of deaths for all infants and total deaths in each GA group

From a total of 251,644 infants included in this study, the majority were moderate to late preterm (76.9%) and 45.7% were female. Median (IQR, range) GA was 34 weeks (32-35, 23-36), while mean (SD) birthweight was 2030g (663), which increased with increasing GA group, as expected. Mean (SD) birthweight Z-score was -0.08 (1.06), and 3.7% of infants in this study had a birthweight Z-score of <-2SD. 55% of infants in this study were of LBW (1500-2499g).

The median (IQR, range) number of episodes of care for all infants was 1 (1-1, 1-13), with median (IQR, range) length of hospital stay of 14 days (6-28, 1-527). Median (IQR, range) PMA at discharge was 36 weeks (35-36, 23-85), while median (IQR, range) day of life at discharge was 14 days (7-28, 1-428). 2.6% of infants died before discharge, and of these, 54% died in the first 7 days of life. The majority of infants who died were extremely preterm (<28 GA). Median (IQR, range) PMA at death was 28 weeks (25-33, 23-101), and median (IQR, range) day of life at death was 6 days (2-20, 1-527).

### 4.4.2 Objective 1: How many preterm infants were diagnosed with GORD during admission to a neonatal unit and what are the characteristics of diagnosed infants?

For this objective, the proportion of infants who were diagnosed with GORD according to different sources of data in the NNRD are shown across three GA groups (Table 4.4). Next, PMA at first diagnosis of GORD and day of life at first diagnosis are shown. Finally, characteristics of infants who were diagnosed with GORD are compared with infants with no diagnosis and adjusted and unadjusted odds of being diagnosed with GORD are presented.

**Table 4.4: Diagnosis of GORD from different sources in the database**

| Outcome, n (%) | All infants n=251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n=193,536 |
|---|---|---|---|---|
| **Any record of GORD** | 11,718 (4.7) | 3,951 (22.6) | 5,240 (12.9) | 2,527 (1.3) |
| **Record of GORD from diagnosis at admission** | 1,122 (0.5) | 668 (3.8) | 333 (0.8) | 121 (0.1) |
| **Record of GORD from diagnosis at discharge** | 10,929 (4.3) | 3,685 (21.1) | 4,897 (12.1) | 2,347 (1.2) |
| **Record of GORD from daily diagnoses** | 5,556 (2.2) | 2,017 (11.5) | 2,466 (6.1) | 1,073 (0.6) |

Based on Table 4.4, 4.7% of infants (n=11,718) were recorded with a diagnosis of GORD from one or more of the different sources of information (data from diagnosis at admission, diagnosis at discharge or daily diagnoses). The majority (n=5,240, 44.7%) of them were very preterm infants. From the three sources of records in the database, the majority of recordings of GORD were in the diagnosis at discharge variable, relatively few infants had a recording at admission, and only about half of those with a diagnosis at discharge had an entry of GORD in the record of daily diagnoses.

**Table 4.5: Postmenstrual age (PMA) and day of life at first GORD diagnosis**

| Variable | All infants n= 251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n=193,536 |
|---|---|---|---|---|
| **PMA at first diagnosis (weeks), median (IQR, range)** | 36 (34-38, 24-82) | 36 (32-39, 24-82) | 35 (33-37, 28-70) | 36 (35-38, 32-71) |
| **Day of life at first GORD diagnosis (day), Median (IQR, range)** | 49 (28-75, 1-404) | 76 (50-100, 1-404) | 45 (30-62, 1-277) | 22 (14-35, 1-272) |

From Table 4.5, median (IQR, range) PMA at first GORD diagnosis was 36 weeks (34-38, 24-82) which was similar across all three gestational age groups. The median (IQR, range) day of life at first GORD diagnosis was 49 days (28-75, 1-404), but decreased from a median of 76 days in extremely preterm infants to 22 days in moderate and late preterm infants.

**Table 4.6: Characteristics of infants with and without GORD diagnosis**

| Outcome, n (%) | Diagnosed with GORD n=11,718 | No diagnosis of GORD n=239,926 |
|---|---|---|
| **Total infants** | 11,718(4.7) | 239,926(95.3) |
| **Female** | 4,931(42.1) | 110,156(45.9) |
| **Gestational age,(weeks)±** | 29(27-31,23-36) | 34(32-35,23-36) |
| **Birthweight (g)+** | 1,312(531) | 2,065(649) |
| **Birthweight Z-score+** | -0.08(0.96) | -0.08(1.06) |
| **Length of hospital stay (day) ±** | 64(42-92,2-404 | 13(6-25, 1-527) |
| **Died before discharge** | 137(1.2) | 6,461(2.7) |
| **Postmenstrual age (PMA) at death (weeks) ±** | 37(33-49,24-66) | 28(25-32, 23-101) |
| **Day of life at death ±** | 72(44-153, 7-286) | 6(2-19, 1-527) |
| **Postmenstrual age (PMA) at discharge (weeks) ±** | 37(36-40, 29-82) | 36(35-36, 23-85) |
| **Day of life at discharge±** | 64(41-91, 1-404) | 14(6-25, 1-428) |

± Median (IQR, range), + Mean (SD)

Based on Table 4.6, when compared with those with no GORD diagnosis, infants who were diagnosed with GORD were born at a lower GA and lower birthweight. Infants with GORD also stayed longer in hospital than those without GORD.
Only a smaller proportion of infants who had record of GORD diagnosis died before discharge, with much older PMA and day of life at death. For those who survived to discharge, infants with a GORD diagnosis were discharged at a later PMA and later day of life.

Next, Table 4.7 shows the unadjusted and adjusted odds ratios for the association between infant characteristics and GORD diagnosis.

**Table 4.7: Unadjusted and adjusted odds ratio for the association between infant characteristics and GORD diagnosis**

| Variable | Diagnosis of GORD | | | |
|---|---|---|---|---|
| | **Unadjusted OR (95% CI)** | **p-value** | **Adjusted* OR (95% CI)** | **p-value** |
| **Female** | 0.86 (0.82 to 0.89) | p<0.001 | 0.80 (0.78 to 0.84 | p<0.001 |
| **Gestational age:** | | | | |
| **32-36 weeks** | 1.00 | | 1.00 | |
| **28-31 weeks** | 11.20 (10.7-11.8) | p<0.001 | 7.40 (6.9-7.9) | p<0.001 |
| **<28 weeks** | 22.04 (20.9-23.2) | | 11.89 (11.0-12.9) | |
| **Birth weight <1500g** | 9.77 (9.4-10.2) | p<0.001 | 1.93 (1.8-2.1) | p<0.001 |
| **Birthweight Z-score < - 2SD** | 0.83 (0.74-0.92) | p<0.001 | 0.74 (0.66-0.82) | p<0.001 |

OR, Odds ratio; 95% CI, 95% Confidence Interval

*Odds ratios adjusted for all other variables in table

Table 4.7 shows that the odds of female infants being diagnosed with GORD was significantly lower than that of male infants in this cohort (adjusted OR (AOR)) =0.80, 95% CI (0.78 to 0.84, p<0.001). Very preterm infants and extremely preterm infants had higher odds of being diagnosed with GORD compared to moderate-late preterm infants, with an adjusted OR (95% CI) of 7.40 (6.9-7.9) and 11.89 (11.0-12.9) respectively.

Infants with a birthweight of <1500g also had a significantly higher odds of being diagnosed with GORD than those born heavier (AOR=1.93, 95% CI 1.8-2.1, p<0.001). However, infants with a birthweight Z-score of less than -2 SD had significantly lower odds of having a GORD diagnosis (AOR=0.74, 95% CI 0.66-0.82, p<0.001).

### 4.4.3 Objective 2: How many preterm infants were prescribed anti-reflux medications and feed thickener and what were these infants' characteristics?

For this objective, the proportion of infants according to GA group who ever received anti-reflux medications during admission and at discharge are shown, followed by information pertaining to its use which are PMA and day of life at first prescription and number of days of use. Characteristics of preterm infants with and without anti-reflux and feed thickener prescriptions are presented with the adjusted and unadjusted odds of receiving these medications.

**Table 4.8: Prescription of anti-reflux medications by GA group**

| Outcomes, n (%) | All infants n=251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n=193,536 |
|---|---|---|---|---|
| **Received anti-reflux medications** | 30,924 (12.3) | 8,634 (49.3) | 12,812 (31.6) | 9,478 (4.9) |
| **Received anti-reflux medications at discharge** | 14,535 (5.8) | 4,352 (24.9) | 6,206 (15.3) | 3,977 (2.1) |

Table 4.8 shows that 12.3% of all infants were recorded to have received one or more days of any anti-reflux medications during admission and 5.8% of infants were recorded to receive anti-reflux medications at discharge. The majority of infants who received anti-reflux medications during admission and at discharge were very preterm infants, comprising 41.4 % and 42.7% of the total number of infants prescribed ever and at discharge, respectively. Almost half of the extremely preterm infants (49.3%) in this cohort ever received anti-reflux medications during admission and 24.9% received it at discharge. The proportions were lower in the other GA groups, particularly so in the moderate and late preterm infants.

**Table 4.9: Postmenstrual age (PMA) at first anti-reflux prescription, day of life at first prescription and number of days of prescription**

| Outcomes, Median (IQR, range) | All infants n=251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n=193,536 |
|---|---|---|---|---|
| **PMA at first anti-reflux prescription, weeks** | 33 (31-35, 23-61) | 30 (28-34, 23-61) | 32 (31-34, 28-60) | 35 (34-36, 32-60) |
| **Day of life at first anti-reflux prescription, day** | 20 (9-35, 1-249) | 34 (18-59, 1-249) | 23 (14-35, 1-210) | 9 (5-16, 1-175) |
| **Number of days of anti-reflux prescription, days** | 15 (6-30, 1-354) | 27 (11-49, 1-354) | 18 (9-30, 1-242) | 7 (4-13, 1-222) |

Table 4.9 shows that median (IQR, range) PMA at first anti-reflux prescription was 33 weeks (31-35, 23-61) and median (IQR, range) day of life at first prescription was 20 days (9-35, 1-249). However, moderate-late preterm infants were prescribed anti-reflux medications at a much earlier day of life compared to the other GA groups. However, they received it for fewer days than other GA groups.

**Table 4.10: Characteristics of infants who did and did not receive anti-reflux medications**

| Outcomes, n (%) | All infants n=251644 | Received anti-reflux medications n=30,924 | Did not receive anti-reflux medication n= 220,720 |
|---|---|---|---|
| **Total infants** | 251,644 | 30,924(12.3) | 220,720(87.7) |
| **Female** | 115,087(45.7) | 13,326(43.1) | 101,761(46.1) |
| **Gestational age, (weeks)±** | 34(32-35, 23-36) | 30(27-32, 23-36) | 34(33-35, 23-36) |
| **Birthweight (g)+** | 2029(663) | 1412(592.78) | 2116(625.57) |
| **Birthweight Z-score+** | -0.08(1.06) | -0.12(1.02) | -0.07(1.06) |
| **Length of hospital stay (day) ±** | 14(6-28,1-527) | 54(31-84,1-527) | 12(5-22,1-385) |
| **Died before discharge** | 6,598(2.6) | 1,069(3.5) | 5,529(2.5) |
| **Postmenstrual age (PMA) at death (weeks)±** | 28(25-33,23-101) | 33(29-38,23-101) | 27(25-31,23-58) |
| **Day of life at death ±** | 6(2-20,1-527) | 38(19-74,1-527) | 4(2-12,1-211) |
| **Postmenstrual age (PMA) at discharge (weeks) ±** | 36(35-36,23-85) | 37(36-39,25-85) | 36(35-36,23-77) |
| **Day of life at Discharge** | 14(7-28,1- 428) | 54(32-83,1-428) | 13(6-22,1-385) |

* Median (IQR range); + Mean (SD)

Table 4.10 shows that 12.3% of all infants were prescribed anti-reflux medications during their stay and there were fewer female infants who received prescriptions than those who did not. Infants who were prescribed anti-reflux medications had a lower GA, birthweight and birthweight Z-score than those without prescription.

Infants with anti-reflux prescriptions had a longer hospital stay (median 54 days) compared to those without prescription (median 12 days). A larger proportion of infants who received anti-reflux medications died before discharge, but they died at a much later PMA (median 33 weeks) and day of life (median 38) than those without medications use.

For infants who survived to discharge, infants with anti-reflux prescriptions were discharged at around similar PMA as infants without prescriptions (median 37 weeks vs. 36 weeks) but at a much later day of life (median 54).

**Table 4.11: Unadjusted and adjusted odds ratio for the association between infant characteristics and prescription of anti-reflux medications**

| Variable | Received anti-reflux medications | | | |
|---|---|---|---|---|
| | **Unadjusted OR (95% CI)** | **p-value** | **Adjusted* OR (95% CI)** | **p-value** |
| **Female** | 0.89 (0.86 to 0.91) | p<0.001 | 0.83 (0.80-0.85) | p<0.001 |
| **Gestational age:** | | | | |
| **32-36 weeks** | 1.00 | | 1.00 | |
| **28-31 weeks** | 8.95 (8.7-9.2) | p<0.001 | 5.92 (5.69-6.17) | p<0.001 |
| **<28 weeks** | 18.91(18.2-19.6) | | 10.04 (9.52-10.6) | |
| **Birth weight of <1500g** | 8.68 (8.46-8.90) | p<0.001 | 1.98 (1.89-2.06) | p<0.001 |
| **Birthweight Z-score < - 2SD** | 1.15 (1.09-1.22) | p<0.001 | 1.02 (0.95-1.09) | 0.545 |
| OR, Odds ratio; 95% CI, 95% Confidence Interval | | | | |
| *Odds ratios adjusted for all other variables in table | | | | |

Table 4.11 shows that female infants had lower odds of receiving anti-reflux medications compared to male infants (AOR 0.83, 95% CI 0.80-0.85). Infants in younger GA groups had higher odds of being prescribed anti-reflux medications than moderate to late-preterm infants. Infants with a birthweight of <1500g and a birthweight Z-score less than -2 SD also had higher odds of being prescribed anti-reflux medications than those of a higher birthweight (AOR 1.98, 95% CI 1.89-2.06) and higher birthweight Z-score (AOR 1.02, 95% CI 0.95-1.09), respectively, though the latter was not statistically significant.

Similar data to those presented above are shown to describe the use of feed thickener.

**Table 4.12: Prescription of feed thickener by GA group**

| Variable, n (%) | All infants n= 251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n= 193,536 |
|---|---|---|---|---|
| **Received feed thickener** | 4,781 (1.9) | 1,477 (8.4) | 2,182 (5.4) | 1,122 (0.6) |
| **Received feed thickener at discharge** | 1,914 (0.8) | 606 (3.5) | 896 (2.2) | 412 (0.2) |

Table 4.12 shows that 1.9% of all infants received feed thickener during admission and 0.8% of infants received it at discharge. The majority of infants who received feed thickener both during admission and at discharge were very preterm infants.

**Table 4.13: Postmenstrual age (PMA) at first feed thickener use, day of life at first use and number of days of use**

| Variables, median (IQR,range) | All infants n= 251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n= 193,536 |
|---|---|---|---|---|
| **PMA at first feed thickener prescription, weeks** | 34 (32-36,25-70) | 34 (31-37,25-70) | 33 (32-35,29-51) | 35 (34-37,32-51) |
| **Day of life at first feed thickener prescription, day** | 32 (19-55,1-331) | 60 (38-84,6-331) | 31 (21-44,2-156) | 14 (9-25,1-132) |
| **Number of days of feed thickener prescription, days** | 11 (5-21,1-140) | 16 (7-30,1-140) | 12 (6-21,1-117) | 6 (3-11,1-119) |

Table 4.13 shows that the median (IQR, range) PMA at first feed thickener use was 34 weeks (32-36, 25-70). Median day of life (IQR, range) was day 32 (19-55,1-331), but extremely preterm infants first received it much later at a median (IQR, range) of day 60 (38-84, 6-331) compared to older GA groups. This youngest GA group however received feed thickener for a longer duration of time with a median (IQR, range) of 16 days (7-30, 1-140).

**Table 4.14: Characteristics of infants with and without feed thickener use**

| Variables, n (%) | All infants n=251,644 | Received feed thickener n= 4,781 | Did not receive feed thickener n=246,863 |
|---|---|---|---|
| **Total infants** | 251,644 | 4,781(1.9) | 246,863(98.1) |
| **Female** | 115,087(45.7) | 2,067(43.2) | 113,020(45.8) |
| **Gestational age, (weeks)±** | 34(32-35,23-36) | 29(27-31,23-36) | 34(32-35,23-36) |
| **Birthweight (g)+** | 2029(663) | 1342(530) | 2043(659) |
| **Birthweight Z-score+** | -0.08(1.06) | -0.06(0.99) | -0.08(1.06) |
| **Length of hospital stay (day) ±** | 14(6-28,1-527) | 62(40-89,4-385) | 14(6-27,1-527) |
| **Died before discharge** | 6,598(2.6) | 60(1.3) | 6,538(2.7) |
| **Postmenstrual age (PMA) at death (weeks) ±** | 28(25-33,23-101) | 35(32-43,28-66) | 28(25-33,23-101) |
| **Day of life at death ±** | 6(2-20,1-527) | 47(33-78,11-286) | 6(2-20,1-527) |
| **Postmenstrual age (PMA) at discharge (weeks)±** | 36(35-36,23-85) | 37(36-40,29-77) | 36(35-36,23-85) |
| **Day of life at discharge±** | 14(7-28,1-428) | 62(40-89,4-385) | 14(6-27,1-428) |

± Median (IQR, range), + Mean (SD

Table 4.14 shows that infants who received feed thickener had basically the same characteristics as shown for infants who received anti-reflux medication, except that they had a higher birthweight Z-score than those who did not receive feed thickener.

**Table 4.15: Unadjusted and adjusted odd ratios for the association between infant characteristics and feed thickener use**

| Variable | Received feed thickener | | | |
|---|---|---|---|---|
| | **Unadjusted OR (95% CI)** | **p-value** | **Adjusted* OR (95% CI)** | **p-value** |
| **Female** | 0.90 (0.85-0.96) | p<0.001 | 0.87 (0.82-0.92) | p<0.001 |
| **Gestational age** | | | | |
| **32-36 weeks** | 1.00 | | 1.00 | |
| **28-31 weeks** | 9.74 (9.05-10.47) | p<0.001 | 6.91 (6.25-7.64) | p<0.001 |
| **<28 weeks** | 15.8 (14.60-17.11) | | 9.48 (8.39-10.71) | |
| **Birth weight of <1500g** | 7.92 (7.46-8.42) | p<0.001 | 1.73 (1.57-1.90) | p<0.001 |
| **Birthweight Z-score < - 2SD** | 0.88 (0.75-1.03) | 0.014 | 0.81 (0.69-0.96) | p<0.001 |
| OR, Odds ratio; 95% CI, 95% Confidence Interval | | | | |
| *Footnote as in previous tables about adjustment | | | | |

Table 4.15 above also shows that the odds of receiving feed thickener were similar to those seen in infants who received anti-reflux medications, except that infants with birthweight Z-score of <-2SD had a lower odd of receiving feed thickener than those of higher birthweight Z-score (AOR 0.81, 95% CI 0.69-0.96).

### 4.4.4 Objective 3: How was the agreement between diagnosis of GORD and anti-reflux medications use in the neonatal unit and was prescription of anti-reflux medications and feed thickener changed over time?

For this objective, the agreement between diagnosis of GORD and prescriptions of anti-reflux medications and feed thickener as well as number of days of prescriptions for both are shown. This is also presented in a Venn Diagram. Next, prevalence of GORD diagnosis, general prescription of anti-reflux medications and use of feed thickener are presented from 2010 to 2017, overall and by GA group.

**Table 4.16: Agreement between diagnosis of GORD and use of anti-reflux medications and feed thickener**

| Outcomes, n (%) | Diagnosed with GORD n=11,718 | No diagnosis of GORD n=239,926 |
|---|---|---|
| **Any prescription of anti-reflux medications** | 10,728 (91.6) | 20,196 (8.4) |
| **Prescription of anti-reflux medications only** | 8,839 (75.4) | 19,003 (7.9) |
| **Number of days of anti-reflux prescription, median (IQR,range)** | 25 (13-43,1-354) | 10 (5-22,1-273) |
| **Any prescription of feed thickener** | 2,299 (19.6) | 2,482 (1.0) |
| **Prescription of feed thickener only** | 410 (3.5) | 1,289 (0.5) |
| **Number of days of feed thickener prescription, median (IQR,range)** | 13 (6-27) | 9 (4-16) |
| **Combination prescription of anti-reflux medication and thickener** | 1889 (16.1) | 1,193 (0.5) |
| **No prescription at all** | 580 (5.0) | 218441 (91.0) |

Table 4.16 shows that 91.6% of infants who had a recorded GORD diagnosis received anti-reflux medications, while only 8.4% of infants with no recorded GORD diagnosis received anti-reflux medications. Infants with a recorded GORD diagnosis also had a higher number of days of anti-reflux medication use (median 25 days) compared to 10 days in those with no recorded diagnosis. A higher proportion of infants with a recorded GORD diagnosis received feed thickener compared to those with no diagnosis (19.6% vs 1.0%), and infants with a recorded diagnosis also had more days of thickener use. This trend was similarly observed in infants who received anti-reflux medications only, feed thickener only, or a combination of both during admission. There was only 5% of infants with GORD diagnosis who did not receive any prescriptions.

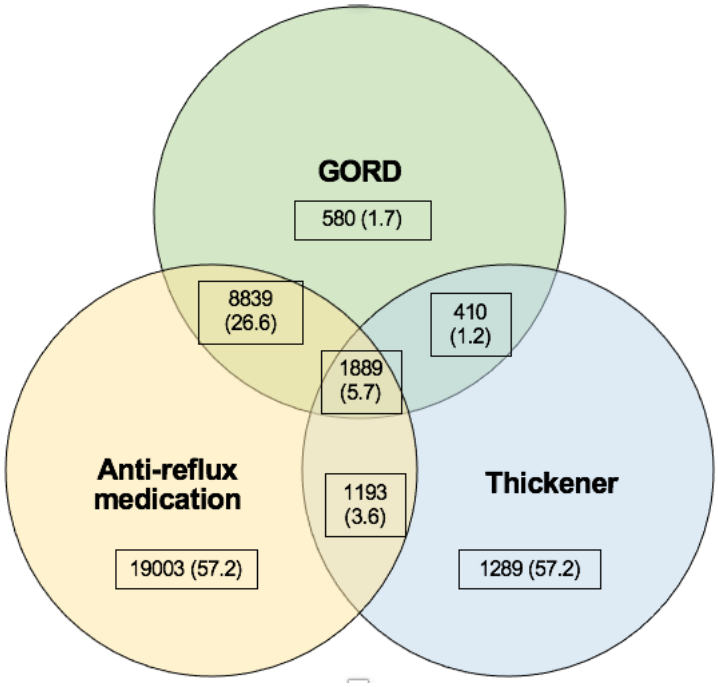
On the other side of assessment, Table 4.17 shows the proportion of infants with GORD diagnosis among infants who have received anti-reflux medications prescriptions.

**Table 4.17: Agreement between the record of anti-reflux medication use and diagnosis of GORD**

| Outcomes, n (%) | Anti-reflux medication use n=30,924 | No anti-reflux medication use n=220,720 |
|---|---|---|
| **Diagnosis of GORD** | 10,728 (34.7) | 990 (0.5) |
| **No diagnosis of GORD** | 20,196 (65.3) | 219,730 (99.6) |

Table 4.17 shows that a majority of infants (65.3%) who had received anti-reflux medications had no recorded GORD diagnosis. Only approximately 35% of infants who received prescriptions had a recorded GORD diagnosis.

Next, Figure 4.3 shows a Venn diagram presenting GORD diagnosis with the use of anti-reflux medications and feed thickener.




| Total infants, n=251644 | n (%) |
|---|---|
| Number of infants who received either anti-reflux medications, feed thickener or had diagnosis of GORD | 33,203 (13.2) |
| Number of infants who did not receive anti-reflux medications/thickener or had diagnosis of GORD | 218,441 (86.8) |

**Figure 4.3: Venn diagram of GORD diagnosis, anti-reflux medication and thickener prescription**

Figure 4.3 shows the prescription of anti-reflux medication, feed thickener and record of GORD diagnosis among infants who had any records of these prescriptions or GORD diagnosis (n=33,203). Approximately 6% of infants had received both prescriptions (anti-reflux medications and thickener) as well had recorded GORD diagnosis. About 27% of infants received anti-reflux medications only (no thickener) and had GORD diagnosis while 57% received anti-reflux medications without GORD diagnosis or thickener prescription. Approximately 2% of infants had GORD diagnosis without any prescriptions, while 1% received feed thickener only with GORD diagnosis. Lastly, about 4% of infants received both prescriptions (anti-reflux medications and thickener) but had no recorded GORD diagnosis.

Lastly, the next three figures below show the prevalence of GORD diagnosis, anti-reflux medications and feed thickener use over the years. This is then followed by the prevalence of GORD diagnosis and anti-reflux medication use according to GA groups, over the years.

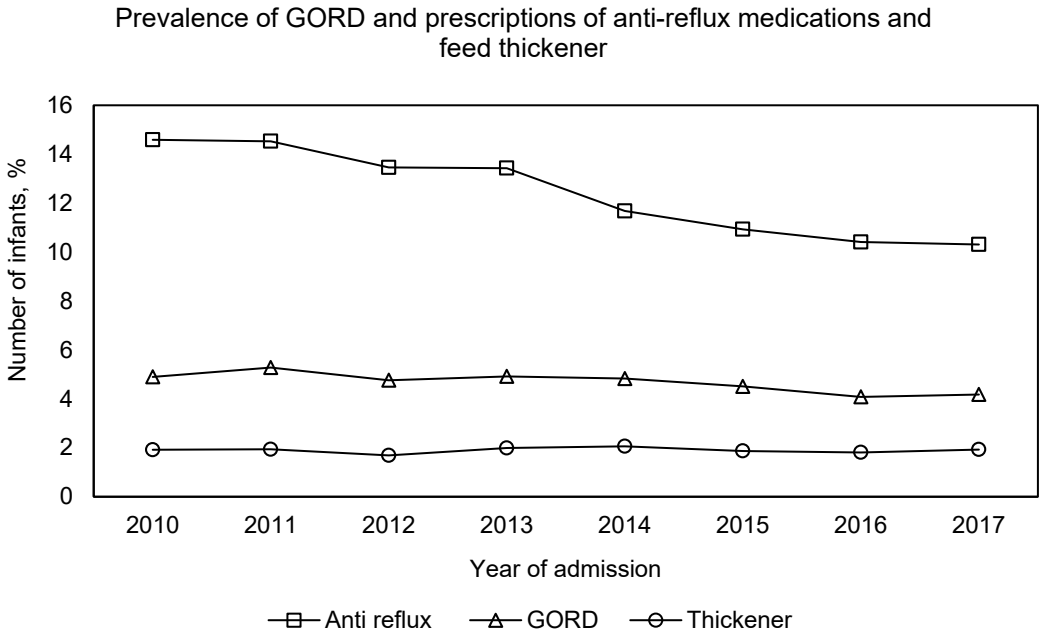



**Figure 4.4: Overall prevalence of GORD diagnosis, prescription of anti-reflux medications and feed thickener use from 2010-2017**

Figure 4.4 above shows the consistently higher proportion of infants with recorded anti-reflux medication use (c.10-14% of infants) compared to GORD diagnosis itself (c.4-5% of infants) and the use of feed thickener (c.2% of infants). The use of feed thickener and the diagnosis of GORD were stable with minimal changes in the prevalence recorded over time. However, the overall use of anti-reflux medications shows a decreasing trend since 2010, with the most rapid decline occurring after 2013.

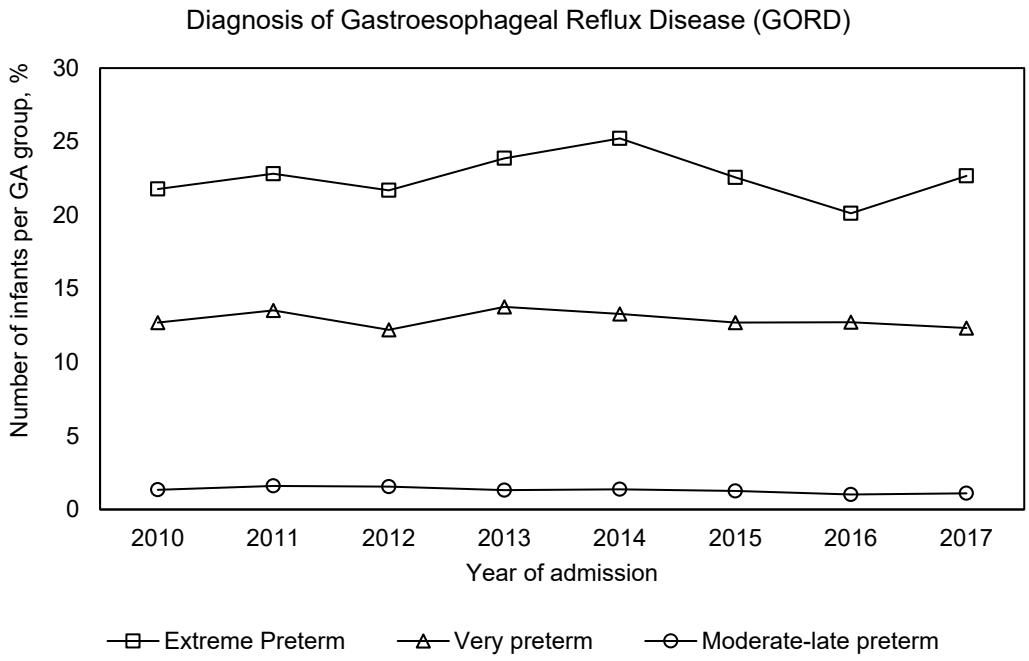



**Figure 4.5: Prevalence of GORD diagnosis by GA group from 2010-2017**

Figure 4.5 shows that more than 20% of extremely preterm infants were recorded with diagnosis of GORD every year since 2010. There were some fluctuations over time but generally prevalence is stable. For other GA groups, the prevalence was consistent since 2010 at approximately 15% and less than 5% of very preterm and moderate-late preterm infants recorded with GORD diagnosis, respectively.

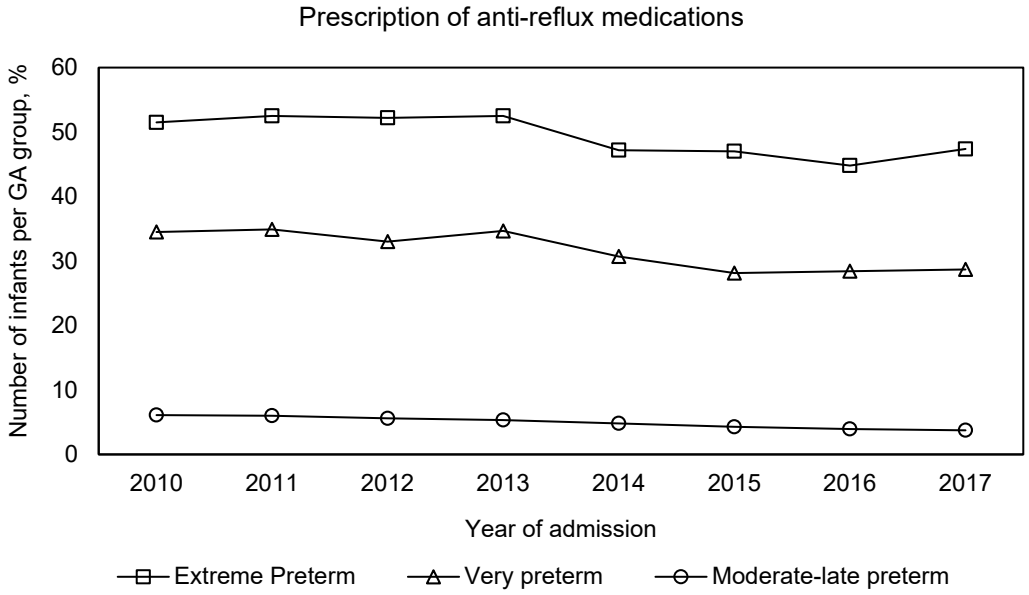



**Figure 4.6: Prescription of anti-reflux medications by GA group from 2010-2017**

Figure 4.6 shows that more than 50% of extremely preterm infants had recorded prescriptions of anti-reflux medication from 2010 to 2013, but the prevalence decreased slightly afterwards. A similar trend is seen for very preterm infants approximately more than 30% of these infants had prescription between 2010 and 2013, but the percentage also decreased after 2013. The use of these medications for moderate-late preterm infants seem consistent over time with less than 10% of these infants recorded to have received it every year, though the prevalence is slowly decreasing over time.

### 4.4.5 Objective 4: What are the types of anti-reflux medications being prescribed specifically in the neonatal units and how was the use of specific anti-reflux medications changed over the years?

For this objective, patterns of individual anti-reflux medications and thickener use are presented which includes: i) most common types of anti-reflux medications prescribed ii) types of anti-reflux medications prescribed first; ii) the number of anti-reflux medication types received; and iii) most common combination of anti-reflux medications received during admission. The denominator for calculating percentages is all infants who received any anti-reflux medication. Feed thickener use is also shown alongside for comparison. Next, the prevalence of different anti-reflux medications prescriptions is shown from 2010 to 2017.

First, Table 4.18 shows most common types of medications prescribed during admission in the neonatal unit.

**Table 4.18: Types of anti-reflux medication and feed thickener prescribed**

| | Received anti-reflux medications | | | | |
|---|---|---|---|---|---|
| **Types of medications/ feed thickener prescribed, n (%)** | **Total infants n= 30,924** | **Extreme preterm infants n=8,634** | **Very preterm infants n= 12,812** | **Moderate and late preterm infants n= 9,478** | **p-value** |
| **Gaviscon** | 17,491(56.6) | 4,467(51.7) | 7,757(60.5) | 5,267(55.6) | <0.001 |
| **PPI** | 4,279(13.8) | 1,736(20.1) | 1,744(13.6) | 799(8.4) | <0.001 |
| **H2RA** | 16,115(52.1) | 5,533(64.1) | 6,426(50.2) | 4,156(43.9) | <0.001 |
| **Prokinetics** | 12,865(41.6) | 4,231(49.0) | 5,503(43.0) | 3,131(33.0) | <0.001 |
| **Feed thickener** | 3,082(10.0) | 1,153(13.4) | 1,423(11.1) | 506(5.3) | <0.001 |

PPI, Proton-pump inhibitor

H2RA, H2 receptor antagonists

Table 4.18 shows that of all infants in the cohort who received anti-reflux medications, majority about 57% had received Gaviscon, followed by H2RA, prokinetics, PPI and feed thickener. Based on GA group, majority of extreme preterm infants received H2RA (64%), while majority of other preterm groups received Gaviscon. The proportion of specific types of anti-reflux medications received in general (from total population in the study) and based on GORD diagnosis is available in Appendix 9.

**Table 4.19: Types of anti-reflux medications prescribed first**

| | Received anti-reflux medications | | | |
|---|---|---|---|---|
| **Types of medications/ feed thickener prescribed first, n (%)** | **Total infants n= 30,924** | **Extreme preterm infants n=8,634** | **Very preterm infants n= 12,812** | **Moderate and late preterm infants n= 9,478** |
| **Gaviscon** | 13,899 (45) | 2,892 (33.5) | 6,265 (48.9) | 4,742 (50) |
| **PPI** | 1,344 (4.4) | 432 (5.0) | 571 (4.5) | 341 (3.6) |
| **H2RA** | 11,910 (38.5) | 4,124 (47.8) | 4,400 (34.3) | 3,386 (35.7) |
| **Prokinetics** | 8,670 (28.0) | 2,594 (30.0) | 3,735 (29.2) | 2,341 (24.7) |
| **Feed thickener** | 1,061 (3.4) | 316 (3.7) | 546 (4.3) | 199 (2.1) |
| **PPI, Proton-pump inhibitor** | | | | |
| **H2RA, H2 receptor antagonists** | | | | |

Table 4.19 shows that of all infants in the cohort who received anti-reflux medications, 45% had received Gaviscon first, followed by H2RA, prokinetics, PPI and feed thickener. Based on GA group, the majority of extremely preterm infants

received H2RA first (47.8%), while the majority of very preterm (48.9%) and moderate-late preterm infants received Gaviscon first (50%).

Table 4.20 shows the number of anti-reflux medication types received by total infants and also according to the GA group.

**Table 4.20: Number of anti-reflux medication types received**

| | Received anti-reflux medications | | | |
|---|---|---|---|---|
| **Number of different types of medications and/or feed thickener received, n (%)** | **Total infants n= 30,924** | **Extreme preterm infants n=8,634** | **Very preterm infants n= 12,812** | **Moderate and late preterm infants n= 9,478** |
| **One type** | 17,129 (55.4) | 3,744 (43.4) | 6,740 (52.6) | 6,645 (70.1) |
| **Two types** | 8,529 (27.6) | 2,822 (32.7) | 3,802 (29.7) | 1,905 (20.1) |
| **Three types** | 4,501 (14.6) | 1,693 (19.6) | 1,994 (15.6) | 814 (8.6) |
| **All types** | 765 (2.5) | 375 (4.3) | 276 (2.2) | 114 (1.2) |
| **Combination of anti-reflux and thickener** | 3,082 (10.0) | 1,153 (13.4) | 1,423 (11.1) | 506 (5.3) |
| **Anti-reflux only** | 27,842 (90.0) | 7,481 (86.6) | 11,389 (88.9) | 8,972 (94.7) |

From Table 4.20, the majority of infants who received anti-reflux medications received only one type of anti-reflux medication (55.4%), 90% of infants had anti-reflux medications only without thickener and only 10% received a combination of anti-reflux medications and thickener. This pattern of medications types received is consistent throughout all GA groups.

Table 4.21 shows the proportion of infants who received most common combination of anti-reflux medications types.

**Table 4.21: Most common type ( if only one ) or combination ( two or three) of anti-reflux medications received**

| Received anti-reflux medications | | | | |
|---|---|---|---|---|
| **Specific type/combination of medications received by the majority of infants, n (%)** | **Total infants n= 30,924** | **Extreme preterm Infants n=8,634** | **Very preterm infants n= 12,812** | **Moderate and late preterm infants n= 9,478** |
| **Gaviscon only** | 8,627 (28.0 | 1,405 (16.3) | 3,718 (29.0) | 3,504 (37.0) |
| **H2RA & Prokinetics** | 3460 (11.2) | 1,163 (13.5) | 1,461 (11.4) | 836 (8.8) |
| **Gaviscon, H2RA & Prokinetics** | 3,003 (9.7) | 1,027 (11.9) | 1,392 (10.9) | 584 (6.2) |
| PPI, Proton-pump inhibitor | | | | |
| H2RA, H2 receptor antagonists | | | | |

Table 4.21 shows that when only one type of anti-reflux medication was used, the majority of infants received Gaviscon rather than other medications. When two types of medications were used, the majority of infants received the combination of H2RA and prokinetics rather than other combinations. Where three types of medications were used, the majority of infants received a combination of Gaviscon, H2RA & Prokinetics.

Lastly, Figure 4.7 shows the trend of prescription of different anti-reflux medications from 2010-2017.

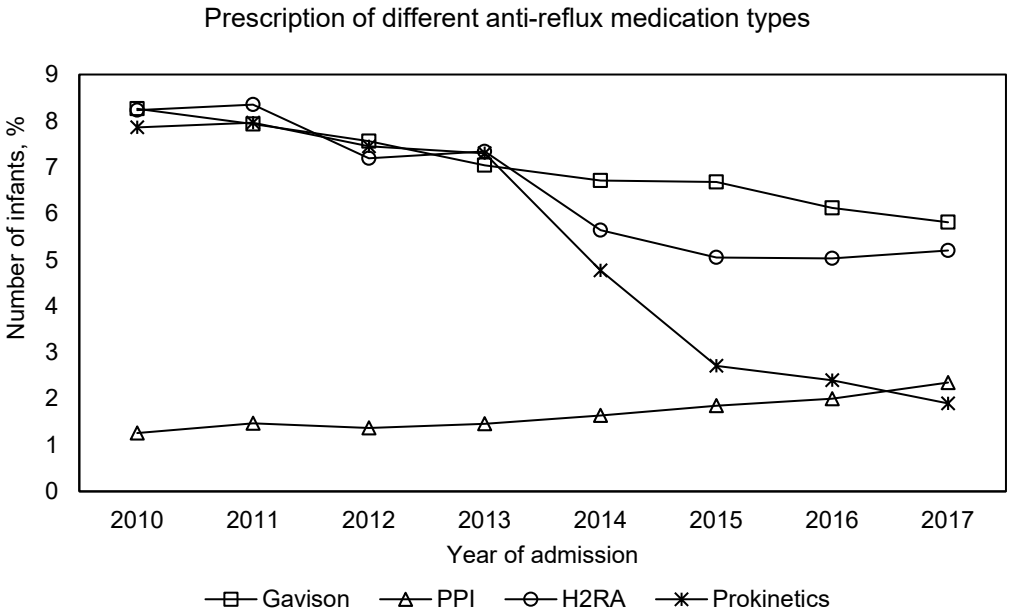



**Figure 4.7: Trend of prescription of different anti-reflux medications**

Figure 4.7 shows that from 2010 to 2013 the prevalence of use of Gaviscon, H2RA and prokinetics was similar, and declining slightly, with approximately 7-8% of infants recorded to have received these prescriptions. However, after 2013, prevalence of use of prokinetics dramatically fell and continued to decrease until 2017 when only about 2% of infants were prescribed prokinetics. Prescribing of H2RA also showed a decrease in use though not as rapid, with use recorded in ~6% of infants in 2014 and a relatively stable percentage after that. Gaviscon showed the slowest decline but prevalence of use also continued to decrease until 2017. On the other hand, the proportion of infants prescribed a PPI showed an increasing trend from 2012 until 2017, although the proportion of infants using this medication was lower than other types of medication.

## 4.5 DISCUSSION

In this study, the proportion and characteristics of preterm infants (23-36 weeks GA) who were recorded with a diagnosis of GORD, anti-reflux medication and feed thickener use during admission until discharge from the neonatal units in England and Wales from 2010 until 2017 were shown. A median number of episodes of care was 1 and the median (IQR) length of hospital stay was 14 days (6-28). Approximately 80% of these infants were discharged home, while about 3% died before discharge. Among infants who died before discharge, 54% died on day 1-7 of life (early neonatal death) of whom about 62% were extremely preterm infants.

### 4.5.1 Diagnosis of GORD among preterm infants

A wide range of clinical signs/symptoms amongst preterm infants are linked to GORD but none are pathognomonic making it difficult to diagnose clinically. In this study, 5% of all infants had a record of GORD which mostly consists of very preterm infants as compared to the other GA groups. The majority of recordings of GORD were retrieved from the diagnosis at discharge variable rather than from daily diagnoses and diagnosis at admission. It was unexpected to find that fewer entries were found in the daily diagnosis variable. This is potentially due to the different ways in which the diagnoses were confirmed in the neonatal unit and how long it takes to decide on the diagnosis. For example, some clinicians might prefer to make a diagnosis without investigations (242), while some wait to see any improvements after non-pharmacological approaches such as changing feeding volumes or frequency or trial of anti-reflux medications for a few days or weeks. These might explain the lack of diagnoses recorded on daily basis – either the symptoms were

resolved before a diagnosis can be made, or it was only recorded later or at discharge.

In terms of the proportion of infants diagnosed with GORD, the UK survey in 2004 (241) performed among 77 neonatal units in England and Wales showed that GORD was diagnosed in approximately 22% of preterm infants (<34 weeks GA) during the study period of June 2000 to February 2001. In comparison, this study showed a lower proportion of infants of the same GA with GORD at approximately 10% almost a decade later. The former was however an estimated incidence by the clinicians from the neonatal units involved, which might not provide the true prevalence as recorded in the NHS record system.

In the US, a large retrospective study of 18,567 preterm infants of 22-36 GA from 33 NICUs admitted from 2007 until 2010 showed a higher rate than in this study in which approximately 10% of these infants received a diagnosis of GORD (95% CI: 9.8–10.7) according to ICD-9 code. There was however 13-fold variation in GORD rates across participating hospitals ($p < 0.001$) ranging from 2-30% that indicates unpredictability in terms of the true incidence of GORD (170). Consistently, a larger study involving hospitals within the Pediatric Health Information System (PHIS) database in the US between January 2006-March 2013 also reported approximately 14% of preterm infants <35 weeks GA to have received an ICD-9 diagnosis of GORD during admission (240).

Referring to the national survey rates or rates recorded in other countries, the exact burden of GORD among preterm infants is still unknown, which is partially due to the diverse definitions and a wide range of clinical symptoms that are attributed to GORD in these infants (385). Various practices were used by the clinicians in differentiating and deciding on infants' symptoms as either physiological reflux or

pathological reflux. Studies showed that the term "reflux", "acid-reflux", and GORD are often used synonymously by healthcare professionals (212) and there were about 25 ways of defining reflux showed in studies and varied definitions of GORD found (232). Furthermore, GOR is a normal occasion in infants with 2–3 episodes of reflux per hour that is also related to their feeding cycles and determining the diagnosis in this population is basically done based on the clinical reasoning of the clinicians (179).

In this study, the median (IQR) of PMA at first GORD diagnosis was 36 weeks (34-38) which was similarly recorded across all three GA groups. The earliest PMA with recorded GORD was at 24 weeks. This is however clinically or theoretically seen to be too early for a diagnosis, although the infants with the recorded diagnoses at this early PMA were also showed to receive anti-reflux medications in later PMA. Some of these records were also a one-off entry in the system, which could possibly indicate a data entry error. However, in general, as the records for PMA and DOL for GORD diagnosis data were identified from only daily diagnoses variable which helps to identify the exact day and PMA at which GORD was first recorded, this shows that GORD was diagnosed a bit later in PMA when infants were more matured. Consistently, extremely preterm infants had their first diagnosis at median DOL 76 as opposed to DOL 22 in moderate and late preterm infants.

This could be related to studies that have shown that preterm infants are noticed to have GOR immediately after their feeding, which is possibly due to gastric distension rather than delayed gastric emptying, although the use of tube feeding or oral feeding has both been shown to have increased the GOR episodes (170,386). In this study, the later PMA at which infants first had GORD diagnosis could be related to the common establishment of a higher volume of feeding around PMA of 35 to 36 weeks in most infants which could have made the GOR events more

apparent. Difficulties with feeding such as vomiting, regurgitation, or discomfort after large volume feeds often manifest only after the establishment of higher feed volumes. Airways are often protected with devices such as endotracheal tubes and breathing supported with additional respiratory support in the early days after birth. Cardio-respiratory events such as episodes of desaturations may manifest later. These signs may be taken to be suggestive of GOR and may prompt trials of treatment and diagnosis of GORD.

Furthermore, during the early weeks of life, different feeding methods, lower or limited feeding volumes and/or the use of intravenous nutrition which bypass their oesophagus might exert protective effects from GORD. Therefore, it's possible that the lower gastric volumes received were less likely to cause GOR episodes among infants during the early days of admission or life. Moreover, the younger premature infants are more likely to have other diagnoses that must be given higher significance such as BPD, apnoea of prematurity, or intraventricular haemorrhage which could lead to oversight of the possible manifestations or diagnosis of GORD.

However, in this study, when comparing infants with GORD and without GORD recorded, those with GORD diagnosis had lower GA at birth (median GA of 29 vs 34. This is consistent with studies that showed that the occurrence of GOR and GORD was higher in preterm than term infants, among extremely preterm infants as compared to more matured preterm infants, as well as in lower birthweight infants (170). This was possibly related to transient lower oesophageal sphincter relaxation (TLESR), a common mechanism of GOR in preterm infants which was closely related to factors such as the infants' immaturity (GA at birth), anatomy, age-specific positions, liquid diet, and feeding methods (179). For example, in terms of physiological or structural maturity, less mature infants have lower oesophageal peristaltic velocity as well as a shorter oesophagus and lower oesophageal

sphincter (LES) which would exacerbate GOR events more than in more matured infants. In addition, among infants of higher GA, they could have been discharged earlier as shown in this study (median length of stay of 13 vs 64 days), therefore did not have a ‘chance’ for the feeding observation and possible GORD experience before discharge home. However, findings also have shown that birthweight Z-score of less than -2 SD had significantly lower odds of having a GOR. This again could have been because of how GORD is being diagnosed in the unit or how an infant is being cared for in the unit. Z-score is generated based on both gender, GA and birthweight of an infant. It is possible that an infant who have a low birthweight z-score, but was born at 35-36 weeks GA, eventhough with a lower weight for the age – but was matured enough to not have suspected GOR. This particular infant could also be able to breastfeed earlier, have fewer medical issues and thus being discharged home sooner – in which all of these could factor up to not having a diagnosis of GORD during the admission.

This is also related to the next point where this study showed that those with GORD diagnosis had longer hospital stay – as consistently shown in other studies as well (168,170). This could be related to the troublesome symptoms and complications of GORD such as frequent regurgitations and severe cardiorespiratory events that cause them to receive more treatment or ventilation support. With these conditions, they might lead to feeding aversion and prolonged reliance on tube feeding which might hinder the infant’s growth and consequently a delayed discharge (168). Furthermore, lower GA at birth and lower birthweight that was found among infants with GORD diagnosis in this study also could have caused the longer length of stay as these infants usually consist of infants with more clinical illness and need more medical interventions which lengthen hospital stay.

Results also showed that there was a higher proportion of infants with no GORD who died before discharge. Therefore, we could say that in this study, the higher number of infants with no GORD diagnosis than those with GORD diagnosis were possibly due to the two extremes of possibilities which are i) higher GA at birth (median GA at birth of 34) that leads to earlier discharge home at median DOL 14 and median PMA at discharge of 36, or ii) a higher proportion of infants who died before discharge as early as median DOL 6 and PMA at death of 28 in which the infants never got to be fed and/or experience GOR symptoms or GORD.

### 4.5.2 Prescriptions for anti-reflux medications and feed thickener

About 12% of all infants in this study were recorded to ever received one or more days of any anti-reflux medications during admission and only ~6% of infants were recorded to receive anti-reflux medications at discharge. This was higher than the record for GORD diagnosis showed previously, which could imply that the use of anti-reflux medications might usually be started without a confirmed diagnosis of GORD or it might be used as a trial of therapy before proceeding to diagnose as GORD and record this diagnosis. Medications could also possibly be prescribed or received only once in which diagnoses were not recorded as the symptoms resolved or alternative diagnosis was found other than GORD.

However, although the record of medications includes all anti-reflux medications (including Gaviscon) used, the rate was lower than shown in a study in the US where approximately 20% of infants <36 weeks GA ever received anti-reflux medications, though this only included H2RA/PPI (240). Additionally, from the total infants who received anti-reflux medications during admission and at discharge in this study, the majority of them were very preterm infants, consistently as shown earlier that almost half of the infants who had GORD recorded were also very

preterm infants. Interestingly, almost half of the extremely preterm infants (49%) in this cohort ever received anti-reflux medications during admission and ~25% received them at discharge. This was similarly shown in another US study in which approximately 25% of extremely preterm infants received anti-reflux medications at discharge (239).

Next, the median PMA at first anti-reflux prescription in this study was 33 weeks, earlier than median PMA first GORD recorded of 36, while similarly, median DOL at first prescription was 20 days, which was also earlier than median DOL 49 when GORD was first recorded. This could again be due to the frequent use of anti-reflux medications as a trial of therapy to diagnose GORD, or this could also indicate that infants who were treated with anti-reflux medications had resolved the symptoms without even being recorded as GORD in the system. Furthermore, the use of medications analysed in this study includes ‘any’ record of medications even for only one day, which means that the higher rate of medication use than GORD recorded was highly possible.

However, as opposed to what that has been demonstrated in a study in the US (240), the median PMA at first anti-reflux medication use in this study increased with increasing GA at birth with median PMA of 30, 32 and 35 weeks respectively for extremely preterm, very preterm and moderate and late preterm infants. This however showed that the use of anti-reflux medications was possibly indicated or prescribed around the time when full enteral feeding was starting to be established and/or a larger volume of milk was received. Therefore, these were the points of time where symptoms associated with feedings such as frequent regurgitation or irritability might commonly be observed, which possibly lead to the prescriptions.

However, DOL at first medication use decreased with increasing GA at birth, in which extremely preterm infants were prescribed anti-reflux medications at a much later DOL as shown as in the GORD diagnosis. Apart from the common use of intravenous nutrition as well as smaller feedings received during early days of life which means fewer GORD-related symptoms were observed, it was also possible that clinicians are being more careful in prescribing medications early for the most vulnerable group of infants, as studies showed adverse effects such as bloodstream infections and necrotising enterocolitis (NEC) that occur with the use of medications such as H2RA (199–201).

As for the duration of medication use, the longest was recorded among extremely preterm infants at a median of 27 days, while in general, infants in this study received it for a median of 15 days. This was comparable to the US study which recorded a median (IQR) treatment duration of also 15 (6–35) days (240). The longer use of medications among extremely preterm infants could be due to their physiology or structural immaturity which makes the symptoms seem to be more severe. Moreover, they also stayed longer in the neonatal unit which opens up to a longer window of opportunity for medication use as compared to those at >32 GA who were discharged sooner.

However, the median duration of 15 days of medication use in this study was actually shorter than proposed by NICE (212), which suggest that in a trial of medication (PPI or H2RA), it should be done for 4 weeks, while NASPGHAN-ESPGHAN (171) suggests a 4-8 week trial of acid suppression (though the trial of PPI is not suggested) if nonpharmacologic measures were unsuccessful or when there is a strong clinical suspicion that GOR is causing complications. This is due to studies that showed no symptom reduction over placebo in infants with treatment periods ranging from 2 to 4 weeks of PPI (198). However, if alginate therapy (i.e.

Gaviscon Infant) was more commonly used in this cohort, a trial period of 1–2 weeks is recommended by NICE especially for breast-fed infants with frequent regurgitation associated with marked distress and this is consistent with what was recorded in this study.

Lastly, as also shown for GORD, infants who received anti-reflux medications also had a lower GA, birthweight and birthweight Z-score while also stayed longer in the hospital (median 54 days). A higher proportion of infants who received anti-reflux medications died before discharge, and they died at a much later PMA (median 33 vs 27 weeks) and DOL (median 38 vs 4). However, for infants who survived to discharge, infants with anti-reflux prescriptions were discharged at a much later DOL (median 54 vs. 13) than those who did not receive anti-reflux medications. This could also mean that the less recorded use of medications was partly due to early discharge or death before discharge which did not allow for any medications to be used or diagnosis made during admission.

For feed thickener use, although at a much lower proportion, the majority of infants who received feed thickener both during admission and at discharge were also very preterm infants. As compared to anti-reflux medication use, PMA and DOL at first use of feed thickener were later, but it was received for a shorter duration. This is probably because the use of feed thickener such as Instant Carobel usually involves mixing the agents into the bottle/cup of expressed breast milk/formula milk which happened when infants can already tolerate oral feeding, as compared to giving medications that can be started earlier. This is however contradicted with what is recommended by the guidelines in which feed thickener is encouraged as an initial step in the management approach of infants with frequent regurgitation or vomiting before proceeding with a trial of medications – which should only be attempted if other non-pharmacological strategies have failed (171).

### 4.5.3 Agreement between GORD diagnosis and anti-reflux medications' use and prevalence of GORD diagnosis and anti-reflux medications' use

In this study, almost 92% of infants who had a recorded GORD diagnosis received anti-reflux medications. On the other hand, approximately 65% of infants who received anti-reflux medications had no recorded GORD diagnosis. This shows that infants with recorded diagnoses in the system are rather ensured to receive the medications respectively as perceived to be needed by the clinician. On the other hand, the recorded prescriptions of anti-reflux medications only do not necessarily mean that infants were ensured to have the confirmed GORD diagnosis in the system. This is again probably due to the common use of these medications as a trial of a therapy to confirm a diagnosis which means that it could be discontinued if symptoms did not improve and alternate diagnoses were suggested. The use of medications as a treatment versus as a diagnostic criterion could not be distinguished in this matter, as the duration of use varied between units and the recommended trial of 4-8 weeks might not be used as a reference.

A survey of UK clinicians showed that 50% of the respondents regularly used clinical features plus therapeutic trials to determine the diagnosis of GORD (241). Trials of anti-reflux medications to establish a diagnosis of GORD is recommended in older infants and children (171) but such therapeutic trials are not recommended in preterm infants because clinical signs and symptoms do not correlate with acidic or non-acidic reflux and the signs improve with time without treatment (197).

Furthermore, the use of Gaviscon Infants, which is a mixture of sodium alginate and potassium bicarbonate that may act as both mild antacids and feed thickener could also be seen by the clinician as feed thickener rather than anti-reflux medications. Therefore, the common use of Gaviscon in the unit might not be perceived as a

treatment that confirms and necessitates recording of a GORD diagnosis, rather it is perceived as a non-pharmacological approach used to relieve GOR symptoms.

Infants with a recorded GORD diagnosis also had a higher number of days of anti-reflux medication use (median 25 days) as compared to 10 days in those with no recorded diagnosis. This further confirms our earlier assumption that medications recorded were used for trial or diagnostic approach rather than as a treatment, in which shorter duration was shown, probably indicating that symptoms could have been reduced, so the medications were discontinued and hence diagnosis was not recorded.

On the contrary, there were also infants with the recorded diagnosis but did not receive anti-reflux medications (8%) and about 5% who did not receive either medications or feed thickener. This is probably due to data error which is possible in any medical records system, or it could be due to the differences in approach taken by clinicians in managing GORD. For example, some clinicians prefer to use a non-pharmacological approach in relieving GORD-related symptoms, and some might also prefer to think of GORD as a self-resolving condition and the possibility of symptoms improvements due to increasing age or maturity, hence no medications were prescribed.

The non-parallel in the rate of medication use and diagnosis of GORD was also translated consistently in the trend of prevalence observed from 2010 to 2017 in which there was always a much higher proportion of infants with recorded anti-reflux medication use (about 10-14% of infants every year) compared to GORD diagnosis (about 4-5% of infants) and the use of feed thickener (about only 2% of infants). Despite unclear symptoms or even diagnostic criteria used in determining GORD

among preterm infants (232), the rate of the diagnosis of GORD was stable with only minimal changes recorded over time.

Furthermore, based on the GA group, consistently > 20% of extremely preterm infants were recorded with a diagnosis of GORD which peaked in 2014 and dropped rapidly afterwards while other groups had consistent prevalence. However, for anti-reflux medications use, while >50% of extremely preterm infants had recorded anti-reflux medication uses from 2010 to 2013, the prevalence decreased slightly afterwards. A similar trend is also seen for very preterm infants. The fall in the use of anti-reflux medications was observed in general since 2011, with the most rapid decline occurring after 2013.

### 4.5.4 Types and trends of anti-reflux medications prescriptions in neonatal units

In this study, from the total number of infants who received anti-reflux medications, about 57% had received Gaviscon, but according to the GA group, 64% of extremely preterm infants received H2RA while the majority of infants in other preterm groups received Gaviscon. This is consistent with the further analysis that showed 45% of infants who received medications had been given Gaviscon first with the majority of extremely preterm infants received H2RA first while the majority of infants in the older GA group received Gaviscon first (50%). This is probably due to the different preparation of these medications in which Gaviscon is mixed in the infants' oral feeding (bottle-fed), which is more common in mature infants, while ranitidine can be given by intravenous injection.

Gaviscon has been shown in small studies in 2010 and 2011 to decrease GOR episodes, total oesophageal acid exposure (224) as well as lessened the frequency

of regurgitation (225). There was also a lack of reported side effects reported for Gaviscon which probably explains its high use in infants as also shown in a clinicians' self-reported survey study in 2018 in which almost 60% from 207 all level neonatal units in the UK used Gaviscon, followed by H2RA (53%) (242).

If one type of anti-reflux medication was used, the majority of infants received Gaviscon, while the combination of H2RA and prokinetics were used if two types were received. PPIs were the least used medications in the neonatal units in this study. It was alarming to note that the use of prokinetics was preferred than PPIs as shown in this cohort, considering that the warning regarding contraindicated use of this agent for infants <12 months old was issued by the FDA since 2009 before the European Medicines Agency (EMA) statement in 2013 (171). It was also clearly stated that their potential side effects counterweigh the possible benefits of these medications for the treatment of GORD (387).

In addition, parallel to what has been discussed on the general prevalence of anti-reflux medication use earlier, from 2010 to 2013, >7% of infants had the prescription of Gaviscon, H2RA and prokinetics similarly. The rate declined rapidly afterwards especially for prokinetics and H2RA and a slight decrease was observed for Gaviscon. This could be explained by the increasing evidence in the use of PPI and H2RA which started to emerge around 2010 to 2013 suggested that they were no better than placebo and may have adverse side effects including a high risk of lower respiratory tract infections, necrotising enterocolitis and other infections (198,201,216,388). This was also alerted in the earlier guideline in 2009 (387). Gaviscon, perhaps seen as more innocuous due to lack of evidence of such associations continues to be used frequently. However, as for PPI, despite the increasing evidence of harm, a slow and steady increasing trend was seen from

2012 until 2017, possibly used as the alternative to H2RA in some units, although the rate was the lowest among other medications.

A study conducted by Omari et al. (213) showed that omeprazole, a PPI, is effective in reducing the frequency of acid reflux episodes and oesophageal acid exposure but has no impact on clinical signs/symptoms in preterm infants. Moore et.al (214), showed that omeprazole reduced the reflux index as compared to placebo, but changes in clinical features were the same in both groups. These findings are similar to studies using other PPIs such as lansoprazole and esomeprazole (215,216). However, both H2RA and PPI were suggested as treatment options for symptoms relief and mucosal healing for GORD in the guideline published in 2009 (387) and 2018 (171). NICE (212) in 2015 also released the updated guideline on the management of GORD and the pharmacological strategies implying that a 4-week trial of a PPI or H2RA can be considered for infants with overt regurgitation associated with either (one or more) unexplained feeding difficulties, distressed behaviour or faltering growth.

As for prokinetics, after the EMA's warning in 2013 on the risk of neurological adverse for metoclopramide, in 2014, the Medicine and Healthcare products Regulatory Authority (MHRA) announced that there was a risk of adverse cardiac events with the use of domperidone (171). Therefore, it could be postulated that the statements by both EMA and MHRA were taken seriously in which the rate of prokinetics prescriptions declined and almost reaching only 2% in 2017.

## 4.6 CONCLUSION

This study shows that the diagnosis of GORD in neonatal units in England and Wales was consistent over time, although the rate was lower than the use of anti-reflux medications in general. Many infants were reported to receive anti-reflux medications although no diagnosis was made during admission or at discharge. However, after 2013, a sudden decline in most medications' use especially prokinetic agents and H2RA was observed, possibly linked to increasing awareness of the adverse effects and lack of efficacy of these medications for preterm infants. While all anti-reflux medications were unlicensed to use in infants, guidelines providing the indications for medication use were often unclear and can be disputing.

Furthermore, while most guidelines also do not commend the use of pharmacological therapies for GORD, recommendations for managing GORD in infants contradicts with some were against the use of acid suppressants and others proposing a trial of such medication. In the recent NASPGHAN-ESPGHAN guideline (171), the recommendation for the trial of acid suppression for 4-8 weeks is suggested for infants with unimproved or recurred symptoms after trying a non-pharmacological approach. This guideline however does not specify the recommendation for preterm infants or infants admitted to the neonatal unit.

The wide range of morbidities and clinical symptoms among these infants due to prematurity and illnesses might masquerade the existing symptoms pertaining to GORD which makes the identification of GORD diagnosis even harder. Additionally, when there are already high concerns regarding commonly diagnosed conditions in preterm infants such as late-onset sepsis and NEC in relation to feeding, the use of anti-reflux medications such as H2RA and PPI without clear indications even with

increasing evidence of the said adverse effects could put these infants at higher risk than where they already are.

### 4.7 STRENGTHS AND LIMITATIONS

This study has its strengths and limitations. Firstly, it is a large database study in which the robustness and validity of NNRD data have been previously demonstrated and it has been used for many other purposes such as national audit and quality improvement projects (382). Over 250000 infants were included in this study, representing the vast majority of neonatal unit admissions in England and Wales from 2010 to 2017. In addition, to our knowledge, this is the first and largest attempt in analysing the prevalence of GORD diagnosis as well as the prescriptions of anti-reflux medications and thickener use in England and Wales involving 200 units contributing data to the study. The results provide valuable information on the use of anti-reflux medications in a large population over a long period.

Several limitations identified in this study are that firstly, there were about 9500 infants with missing data for variables such as GA, sex, birthweight, extreme birthweight Z-score, and missing days and episodes of care which were excluded.

Secondly, the diagnosis of GORD was recorded from three data sources which are diagnosis at admission, at discharge, as well as in the daily care variable. However, the PMA at first diagnosis and DOL at first diagnosis could be extracted only from daily care variables as it can provide the exact time from birth to the point when the diagnoses were first recorded. This means that for infants who only have recorded diagnosis from admission or discharge variables, the information on PMA and DOL at first diagnosis was not included which may limit the actual representation of all infants with GORD diagnosis in this study. However, based on the results, the

median PMA of total infants and throughout the GA group was quite consistent. Therefore, it is likely that very minimal differences could have been seen even with the inclusion of all data sources.

The use of the NNRD as source data also has some limitations as it is not used for primary prescribing and diagnoses are not recorded in a standardised manner such as using ICD codes. There is a risk of data entry errors and missing data. The lower prevalence in NNRD data than the use of anti-reflux medications could also reflect diagnoses not recorded or may represent the lack of formal diagnosis. There was also a lack of data provided in the database which could further specify the nature of anti-reflux medication prescriptions such as the frequency or dosages of medications given.

In summary, findings suggest that there are higher prescriptions of anti-reflux medications among preterm infants that might be occurring in the neonatal units. Clear guidelines for diagnosing GORD and for rationalising the pharmacological management of GORD are required. It is crucial that the health practitioners understand and are able to differentiate the physiological and pathological GOR in order to avoid overtreatment and overprescription of medications.

To assure that changes in practice are possible, we need a greater understanding of the most effective non-pharmacological therapies for managing GORD among preterm infants, as well as concrete evidence on the associated adverse effects from H2RA and PPI use in the UK through randomised controlled trial or a large national observational study. A continuation national database study (using NNRD) on the use of anti-reflux medications and adverse effects among infants admitted to neonatal units has been planned and approved to be conducted (approval documents available in Appendix 10).

From this study, we found that although there was high use of anti-reflux medications in the neonatal units, there was also a decreasing trend in some medications' prescriptions while the diagnosis of GORD was stable over time. Therefore, in the next chapter, I will present the self-reported practice of health practitioners on the diagnosis and management of GORD in preterm infants as well as their views on anti-reflux medication use. This is followed by exploring parents' perspectives on the use of different strategies in treating infants with GORD and both sides' views on the conduction of clinical trial for the management of GORD in preterm infants.

# CHAPTER 5: THE MANAGEMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD) AMONG PRETERM INFANTS IN NEONATAL UNITS: HEALTH PRACTITIONER AND PARENTS' PERSPECTIVES

## 5.1 INTRODUCTION

Gastroesophageal reflux disease (GORD) occurs when physiological reflux causes troublesome symptoms such as irritability, back-arching, poor feeding and/or respiratory disturbance, including apnoea. Many infants in NICU are treated for GORD (239) though high-quality evidence on effective pharmacological and non-pharmacological management strategies for this population are still lacking (172).

Moreover, no gold standard tool exists for the diagnosis of GORD in infants and children yet. This poses challenges for the health practitioners in determining the best way to care for infants with presumed GORD. It leads to a wide variation in diagnostic and management strategies found in studies in many countries, including the UK (242).

The most current guidelines for the management of GORD among the paediatric population is by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) combined (March 2018) (171) which is the updated version of the one published in 2009. In the UK, the guideline that is targeted for healthcare practitioners and carers/families of children and young people (under 18s) with GORD is regularly updated by the National Institute for Health and Care Excellence (NICE) (212). Although neither of these guidelines has a specific recommendation for infants in the neonatal unit or preterm infants, they agree to start with the non-pharmacological approach for the treatment and to avoid anti-reflux medications (i.e. PPI/H2RA) to treat visible regurgitation in

otherwise healthy infants or those that present with isolated symptoms. Ultimately, despite the emergence of evidence questioning the need to use anti-reflux medications in preterm infants and the possibility of adverse effects related to their use, anti-reflux medication use is still widespread (229,389). One of the reasons leading to the increased use of medications is parents' demand for their use, influenced by external information received regarding GORD (390). It has been shown that parent's perception of the need to use medications was influenced by the 'GORD' diagnosis label used by clinicians, even if the medications are known not to be effective.

However, it is not known if this perception might change if the parents are given non-pharmacological alternatives by the attending clinician, provided with enough information on possible side effects of medications or infant not receiving definite GORD diagnosis without confirmed tests in the first place. This study, which is a scoping survey undertaken as a patient and public involvement activity (PPI), aims to explore the current practice and perception of health practitioners on the management of GORD among preterm infants as well as the perception of the parents of preterm infants diagnosed with GORD on the treatment of GORD received during admission in the neonatal unit.

This study will first describe the health practitioners' views and self-reported practice regarding the symptoms, diagnosis, and treatment of GORD in preterm infants in a NICU setting. Secondly, it will describe the perception of parents of preterm infants about the use of different management strategies in treating GORD in the NICU. Lastly, it will assess the views from both health practitioners and parents on the feasibility and willingness to participate in the clinical trial considering the pharmacological and non-pharmacological strategies in managing GORD.

## 5.2 STUDY OBJECTIVES

### 5.2.1 Study objectives

1. To investigate current practice (as reported by clinicians) and perspectives of heath practitioner in the diagnosis and management of GORD among extreme and very preterm infants in the neonatal units
2. To investigate the parents' perspectives on the use of medications in the management of GORD for their preterm infants

### 5.2.2 Secondary objectives were:

1. to determine the diagnostic criteria and tests used to establish a GORD diagnosis among preterm infants in the neonatal unit
2. to assess the management strategies (as reported by clinicians) used in preterm infants with GORD in the neonatal unit
3. to determine the perspective of health practitioners on a proposed clinical trial randomising infant into pharmacological or non-pharmacological management for GORD and its feasibility
4. to assess the parents of preterm infants' perspectives on the use of pharmacological and non-pharmacological intervention in the initial management of GORD in neonatal unit and their preferred treatment for the infants
5. to determine the parents' perspective on a proposed clinical trial randomising infant into pharmacological or non-pharmacological management for GORD and their views on infant care and important outcome measures for the trial

## 5.3 METHODOLOGY

### 5.3.1 Study design

A cross-sectional prospective study using an online survey. This survey was undertaken as a patient and public involvement activity (PPI).

#### 5.3.1.1 Questionnaire Development

A 14-item survey for the health practitioners and 12-item survey for parents of preterm infants were developed based on a combination of literature review, clinical guidelines and clinical experience of the neonatologists (part of the research team). It was designed to explore the current practice of health practitioners in handling GORD and parents' view on it. In addition, it also aimed to characterise the future research preferences for clinical trial of GORD management in preterm infants, taking into consideration the perspectives of these two main key stakeholders.

Questions for the health practitioners' survey included consisted of a combination of open-ended, closed-ended and contingency questions that followed some of the closed-ended questions. Closed-ended questions consisted multiple choice (single response/multiple response) and dichotomous (yes/no) questions with a space for free text answer provided for some questions if the option "other" were selected. A copy of both questionnaires is given in Appendix 11.

Six main domains of questions in the health practitioner's questionnaire were:

i. signs and symptoms of GORD

   A list of 17 signs and symptoms were provided where responders could tick all that apply to them. The list was created by a review of literature. Clinical signs/symptoms used to diagnose GORD in such studies were included in this list (Table 5.1).

ii. tests used to diagnose GORD

iii. management strategies for GORD (pharmacological and non-pharmacological approach)

iv. views on a proposed clinical trial for the management of GORD in preterm infants.

v. open-ended question on other views on the management of GORD in preterm infants

vi. demographic information: types of practice and level of neonatal unit on which the respondent was currently working.

**Table 5.1: Clinical signs and symptoms of GORD in clinical trials in preterm infants**

| First author | Year of publication | Vomiting | Regurgitation | Gaging or chocking | Desaturations | Bradycardia | Apnoea | Postprandial events | Stridor | Poor weight gain | Back arching/ head extension | Irritability, fussing | Pain or facial grimacing | Refusal to feed | Abdominal distention | Hiccups | Aspiration pneumonia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Atasay** | 2010 | y | | | y | | | | y | y | | | | | | | y |
| **Ballengee** | 2018 | | y | | y | y | y | | | | y | | | | y | | |
| **Corvaglia** | 2006 | | | | | | | | | | | | | | | | |
| **Corvaglia** | 2010 | | y | | y | | | y | | | | | | | | | |
| **Corvaglia** | 2011 | | | | | | y | y | | | | | | | | | |
| **Corvaglia** | 2013 | | y | | y | | | y | | | | | | | | | |
| **Corvaglia** | 2016 | | y | | | | | y | | | y | y | | | | y | |
| **Davidson** | 2013 | y | | y | y | y | y | | | | | y | y | | | | |
| **Omari** | 2006 | y | | | | | y | | | y | | y | | y | | | |
| **Omari** | 2007 | y | | | | | y | | | y | | y | | y | | | |
| **Orenstein** | 2009 | | | | | | | y | | | | y | | | | | |
| **Ward** | 2010 | y | y | y | | | | | | y | y | y | y | y | | y | y |

The questionnaire was pilot tested by a small sample of consultant neonatologists, clinical trial specialists and a research nurse (n=7). The questionnaire was then revised as per the feedback.

The parents' questionnaire included a combination of open-ended, closed-ended and contingency questions that followed closed-ended questions. The closed-ended questions consisted of multiple choice (single response/multiple response) and numerical rating/Likert rating scales (0-10 and 1-4).

The parent questionnaires were piloted by a panel of 3 parent representatives and revised as per the feedback.

Five main domains of questions were constructed for the parents' questionnaire, which were based on a given scenario of a proposed clinical trial where infants would be randomised to receive anti-reflux medications as their initial GORD management or be managed with the non-pharmacological strategies without anti-reflux medications.

The domains of questions for this cohort's survey therefore could be categorised as below:

i. demographic information
ii. perspectives on the initial approach in the management of GORD: with or without medication use.
iii. preferences on the treatment of reflux symptoms.
iv. views on a proposed clinical trial for the management of GORD in preterm infants.
v. open-ended question on other views/comments on GORD among preterm infants or the proposed clinical trial

### 5.3.2 Study participants

#### 5.3.2.1 Sample size

As this was a scoping survey undertaken as a patient and public involvement activity (PPI), no formal sample size calculation was performed. The participants for the health practitioners' survey were selected based on those who were in the email list (n=20) for an ongoing clinical trial by the same Chief Investigator, had given permission to be contacted for further research and were currently working in neonatal units. Further dissemination was via Twitter ™ (http://www.twitter. com) network of the investigators and their "followers". The target was to receive 100 individual responses.

The parent survey was disseminated via social media platforms (Twitter ™) of the investigators and parent representatives and recognised UK based parent networks including Bliss and @NeoMates. The aim was to receive at least 50 individual responses.

#### 5.3.2.2 Ethical approval

As these were scoping surveys undertaken as a patient and public involvement activity (PPI) to determine individual views and feasibility of further studies, no ethical approval was required. Participation to join and answer the survey was entirely voluntary, and formal consent was not obtained as completion of the online survey was taken as implied consent. The survey was disseminated via social media and did not access any healthcare professionals' details from their workplace. No approach was made via the NHS. The dissemination on social media were via personal accounts of those who supported this work and via the Nottingham Clinical Trials Unit, an organisation that is outside the NHS.

#### 5.3.2.3 Confidentiality

The parents' questionnaire was fully anonymous. For the health care professional survey, an option for the respondent to provide their contact details was provided if they wished to be contacted for any further research. The survey otherwise did not collect any personal information and the respondents were aware that the results will be used for developing further research and publications.

### 5.3.3 Data collection

The surveys were conducted by using online surveys platform at www.onlinesurveys.ac.uk (previously known as Bristol Online Survey or BOS). This is managed by the Joint Information Systems Committee (JISC) – an organisation for digital services and solutions provider for UK's higher education and skills sectors in which the University of Nottingham provides access for the postgraduate students.

The link to the online survey was distributed as described above. The tweet by the research team was shared by more than 50 users, enabling us to reach participants even those from the USA, Turkey, Denmark, Austria, Oman, Australia, Sweden, Saudi Arabia, Spain, Chile, and Brazil.

For parents, Twitter™ was the main tool used for distributing the survey, where the tweet was shared widely by other organisations and groups such as Bliss Baby Charity, Neomates and NCT Charity that leads to the participation of many parents of preterm infants. The way 'retweet' works in the recruitment process is one of the applications of a snowball sampling method whereby one research participant who had the access to the survey link has the potential to reach other users (391). The study period for both surveys was from 21 August 2020 to 22 September 2020.

### 5.3.4 Data analysis

Data are presented as the proportion of responders to each questionnaire item. Responses were excluded if the questionnaire was not completed correctly. Data analysis for each item is based only on valid responses. Missing responses were excluded as appropriate. The questions also consist of the combination of “tick all that apply” and “choose one only”. Therefore, the total percentages would not be equal to 100% for the total responses.

The data analysis was essentially descriptive with multiple choice questions (close-ended and numerical rating scale (4 levels) where values were expressed as frequency and percentages (responds are grouped as categorical data). Questions with numerical rating scale of 11 levels (0-10) were described by frequency, percentage as well as median (interquartile range of scale, minimum and maximum scale) as appropriate.

Free text and responses to open-ended questions are either presented in original wordings/quotes or summarised and encoded with general theme. Frequency and percentages of responses under each theme are presented if responses were more than 10.

Statistical analysis was performed by using STATA 16.0 software (Stata Corp. College Station, TX).

## 5.4 RESULTS

In this section, the population demographic data are presented first, followed by main results which are presented according to the objectives of the study.

### 5.4.1 Recruitment of study participants

One-hundred and fifty-six (n=156) participants responded to the health practitioners' survey. Two did not complete the survey, resulting in a sample of 154 participants. Complete responses were received from 63 participant for the parents of preterm infants' survey. The number of participants in both surveys exceeded initial targets of 100 (health practitioners) and 50 (parents) responders.

### 5.4.2 Demographics of study participants

Limited demographic information was asked to ensure participants were not identifiable from their response and to reduce the survey burden. Table 5.2 shows the demographic characteristics of the health practitioners and parents of preterm infants participated in the survey.

**Table 5.2: Participants' characteristics**

| Health practitioners' Survey | | |
|---|---|---|
| **Characteristics** | **n=154** | **%** |
| **Healthcare professionals** | | |
| Nursery nurse | 1 | 1 |
| Nursery nurse practitioner | 1 | 1 |
| Allied Health Professional | 9 | 6 |
| Nurse | 38 | 25 |
| Advanced Neonatal Nurse Practitioner | 10 | 7 |
| Trainee in Neonatology/Paediatrics | 21 | 14 |
| Consultant Neonatologist/Paediatrician | 74 | 48 |
| **Level of neonatal unit** | | |
| Level 1: Special Care Baby Unit | 3 | 2 |
| Level 2: Local Neonatal Unit | 20 | 13 |
| Level 3: Neonatal Intensive Care Unit | 131 | 85 |
| **Parents' Survey** | | |
| **Characteristics** | **n=63** | **%** |
| **Have a preterm infant** | | |
| Yes | 63 | 100 |
| No | 0 | 0 |
| **Gestational age of infants at birth** | | |
| <28 weeks | 26 | 41 |
| 28-31 weeks | 23 | 37 |
| 32-36 weeks | 14 | 22 |
| **Diagnosis of GORD during admission** | | |
| Yes | 37 | 59 |
| No | 24 | 38 |
| Not sure | 2 | 3 |

Data in Table 5.2 show that 74/154 (48%) of health practitioners involved in this survey were Consultant Neonatologist/Paediatricians, followed by nurses, 38/154 (25%). Most (131/154 (85%) respondents work in level 3 neonatal units (NICU). Among the respondents of the parent survey, 26/63 (41%) have preterm infants who were born at <28 weeks GA and majority at 37/63 (59%) responded that their infants have had a diagnosis of GORD during hospital admission.

### 5.4.3 Objective 1: What are the signs and symptoms perceived to be related to GORD and what tests are used to make a GORD diagnosis?

Signs and symptoms perceived to be related to GORD and the tests used in the usual clinical practice to diagnose GORD (Figure 5.1) are presented from the highest percentage to the lowest percentage (n=154). Free text for “other” are shown for each domain.

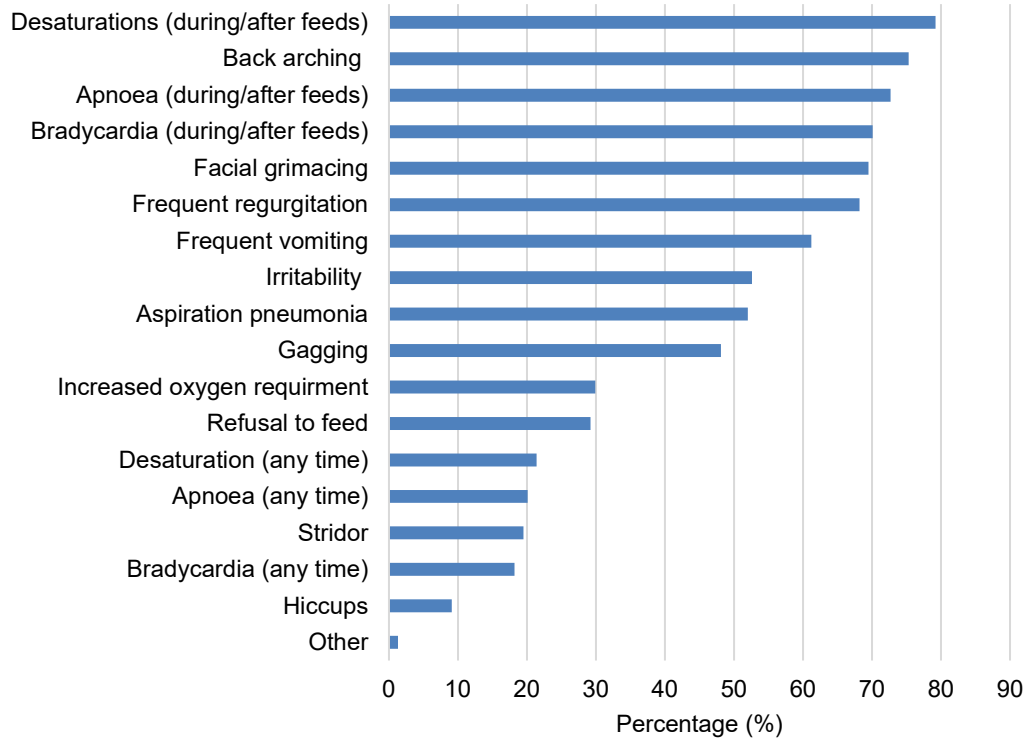



**Figure 5.1: Signs and symptoms perceived to be related to GORD**

Figure 5.1 shows that the highest percentage of the health practitioners believe that desaturations which occur during or after feeds are related to GORD,122/154 (79%), followed by back arching or head extension,116/154 (75%) and apnoea occurring during/after feeds,112/154 (73%). Hiccups, 14/154 (9%) and bradycardia

(any time), 28/154 (18%) were selected by the least number of participants. The free text response of the practitioners, 2/154 (1%) were as below:

- "To me GOR is normal in this population. GORD as a disease would probably be considered if there's poor weight gain and frequent crying although I would diagnose feed intolerance rather than GORD"
- "I believe the GORD is extremely rare in this population. GOR is a self-resolving condition related to prematurity - not a disease."

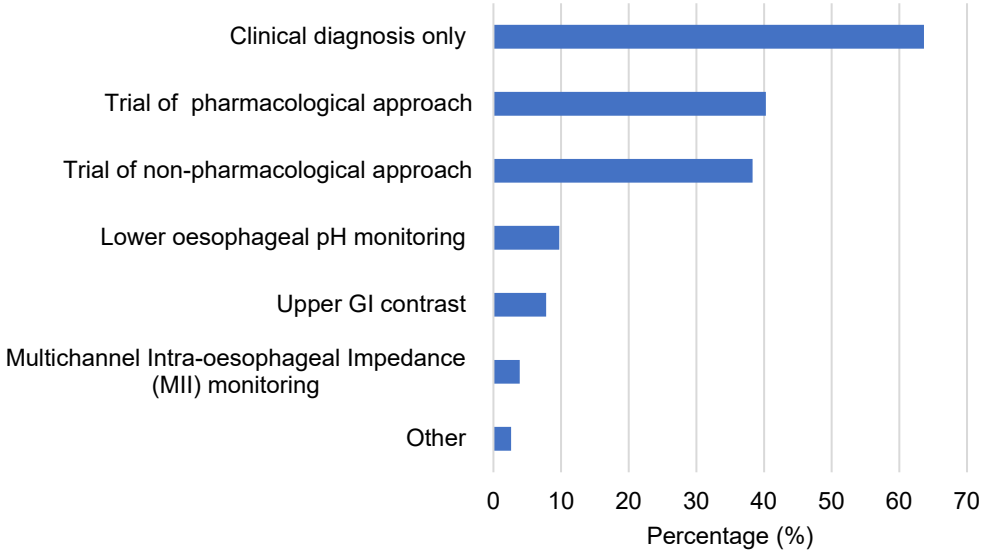



**Figure 5.2: Tests and strategies used to diagnose GORD in usual clinical practice**

Figure 5.2 shows that majority of the health practitioners in this study do not use tests to diagnose GORD routinely. 98/154 (64%) base their diagnosis on clinical features, 62/154 (40%) use response/trial to pharmacological management (anti-reflux medications) as a diagnostic strategy and 59/154 (38%) use response to non-pharmacological management as a diagnostic strategy. Only about 15/154 (10%) use pH monitoring in their usual practice, followed by upper GI contrast ,12/154 (8%) and multichannel intraluminal impedance (MII) monitoring, 6/154 (4%).

Free text responses, 4/154 (3%) included one response that said, “test of allergen free milk (either mother’s milk or formula)”, while three others said that “GOR is very common and I never investigate it”; “self-resolving condition”; and “depends on the doctor’s decision”.

The sub-question that followed was regarding the duration of medication use if they choose a trial of pharmacological management in diagnosing GORD. Results showed that 39/124 (32%) use it for 1 week, 30/124 (24%) would use it for 2-5 days, 28/124 (23%) used it for 1-2 weeks, while 18/124 (15%) use it for more than 2 weeks.

### 5.4.4 Objective 2: What are the main strategies used to manage preterm infants with GORD and which of the non-pharmacological and pharmacological strategies are more commonly practised in neonatal units?

Self-reported responses for the strategies used to manage GORD by the health practitioners are shown in Figure 5.3. The specific types of non-pharmacological and pharmacological strategies used are shown in in Figure 5.4 and Figure 5.5 respectively.

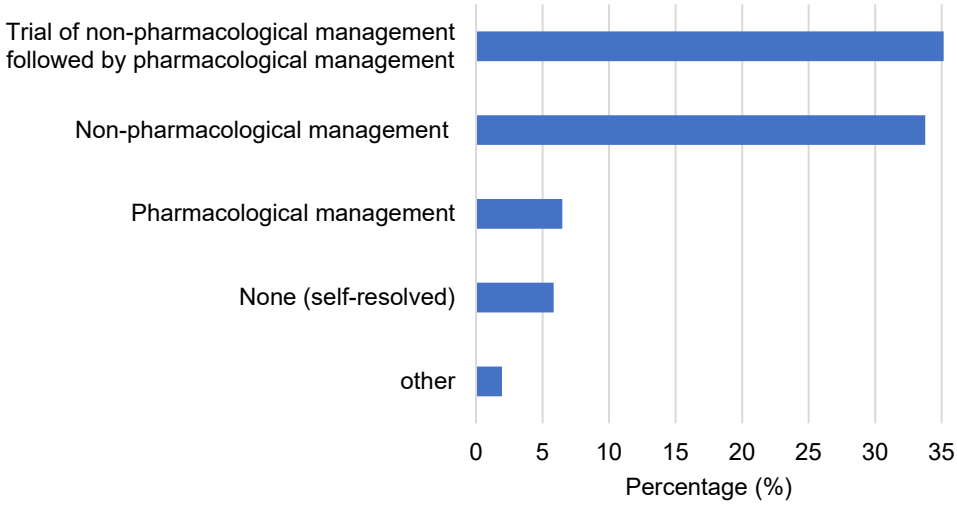



**Figure 5.3: Main strategies used by health practitioners to manage GORD in neonatal units**

As shown in Figure 5.3, 80/154 (52%) of the health practitioners first try non-pharmacological strategies and then proceed with medications, 52/154 (34%) use non-pharmacological management only (no test) and 10/154 (7%) use medications only (no test). In addition, 9/154 (6%) do not use any treatment and consider that the condition is self-resolving, while 3/154 (2%) respondents selected “other” but there were no free text responses to clarify what they meant.

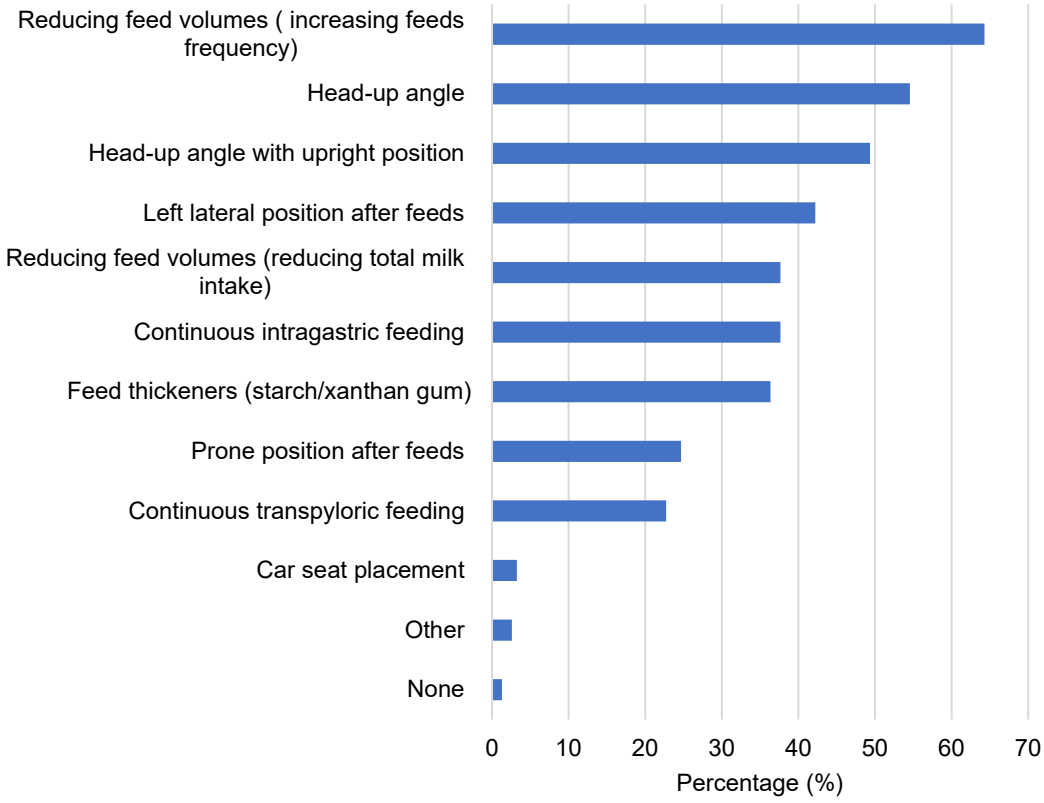



**Figure 5.4: Non-pharmacological strategies used to manage GORD in neonatal units**

Figure 5.4 shows that the majority of the health practitioners 99/154 (64%) reported that they reduce the feeding volumes by increasing feeds frequency as the main non-pharmacological strategy. In addition, among other strategies they used as showed in this survey were the use of positioning as head-up angle, 84/154 (55%) and head-up angle with upright position, 76/154 (49%).

Other strategies that were given as free text responses, 4/144 (3%) were:

- Side lying bottle feeds
- Reducing feed volumes by increasing caloric density
- Trial of allergen free milk
- Gaviscon in feeds

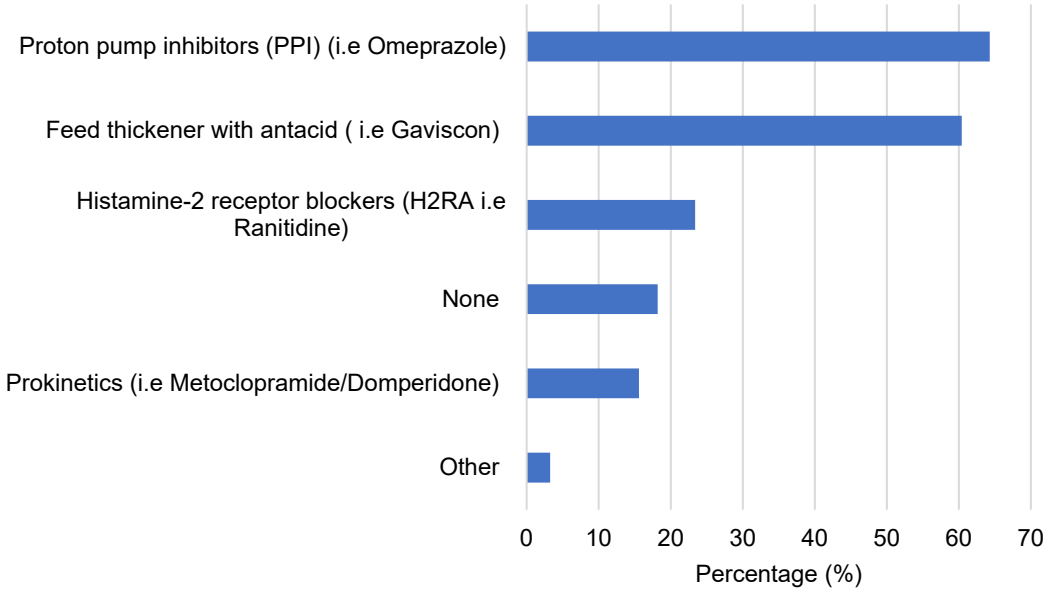



**Figure 5.5: Pharmacological approach in the management of GORD in the neonatal unit**

Figure 5.5 above shows that majority (100/154 (65%) of the health practitioners use PPI to manage GORD, followed by feed thickener with antacid such as Gaviscon (93/154 (60%)). 37/154 (24%) use H2RA, 27/154 (18%) use prokinetics and 28/154 (18%) do not use any medications. Five respondents (3%) selected “other”. Their free text response showed that three of them used prokinetics (erythromycin) and one of them used PPI and H2RA. The numbers are added to the responses for the prokinetic, PPI and H2RA, respectively.

Regarding the duration of medication used to manage GORD, 30/136 (22%) said that the treatment continues until after discharge, 30/136 (22%) answered “other”, 26/136 (19%) continue the treatment for 2-4 weeks, 21/136 (15%) use it only until hospital discharge, while 19/136 (14%) and 10/136 (7%) use it only for 1-2 weeks and for 4-8 weeks, respectively. For those who chose to continue the medications after discharge, free text responses showed that they would continue the medications post discharge until follow-up in clinic/community/next review, 9/30

(30%), “as long as required” or “until GORD resolves”, 3/30(10%), for “few weeks” 1/30 (3%), “depends on baby’s age” 1/30 (3%), while 16/30 (53%) were not related to question/did not answer. Other responses were not reported due to the technical errors of the survey.

### 5.4.5 Objective 3: What is the health practitioners’ perspective on a clinical trial randomising infant into pharmacological or non-pharmacological management for GORD and is it feasible?

In a given scenario of a clinical trial where preterm infants would be randomised into an intervention arm (using non-pharmacological strategies to manage GOR) and control group (pharmacological management), 127/150 (85%) of the participants felt that they would consider participating in the clinical trial, while 23/150 (15%) did not tend to consider for the participation into the clinical trial.

For the infants with criteria as mentioned in the scenario (preterm infants <32 weeks GA) with GOR signs/symptoms, there was an 87% response rate (n=134/154). 75/134 (56%) stated that <10 infants with the criteria could be seen at their unit each month while 57/134 (43%) mentioned ≥10 infants that could probably be seen and 3/134 (2%) were unsure.

The reasons why health practitioners responded that they would not agree to participate are shown in Table 5.3. The number of responses for this question was recorded to be 28, more than the number of responses of those who did not want to consider for the participation in the clinical trial recorded earlier (n=23/150). All written feedbacks were however recorded as it is to take into consideration their qualitative responses. Next, the duration of waiting for responses to non-pharmacological strategies before starting treatment for the intervention arm are

shown in Figure 5.6 and the minimum suggested days of reduction in medication use for the trial's outcome is shown in Figure 5.7. Finally, other views regarding the GORD management in preterm infants <32 weeks GA are shown in Table 5.4 based on the summarised themes of the responses (n=43).

**Table 5.3: Summary of reasons for not agreeing to participate in a proposed trial**

| **Themes** | **n(%)** | **Quotes** |
|---|---|---|
| **Concerns on medications use/rarely use medications in the unit** | 19(68) | "Do not treat reflux in extremely or very preterm infants. Concern about association with sepsis and NEC with acid blockade"<br><br>"Pharmacologic management associated with harm (NEC, nutritional deficiency, increased cost)"<br><br>"If the pharmacological treatment is an antiacid drug, the associated risks (higher NEC and late onset sepsis rates) can overpass the benefits"<br><br>"Rarely use pharmacological management. Last resort" |
| **Prefer other grouping options for trial** | 3(11) | "…This design will still result in the infants in both groups getting treated and too little difference between groups to determine risks and benefits. You need a design that locks babies in one group out of treatment for a long enough period to allow meaningful comparison. Then I would be more interested"<br><br>"I would say non-pharmacological in both and pharmacological in one as intervention and placebo in other one as control"<br><br>"Do not consider pharmacological treatment to be a control" |
| **Miscellaneous** | 6(21) | "My hospital is not supportive enough of clinical research, but if I were at an academic centre, then, definitely"<br><br>"Depends on severity of infants symptoms"<br><br>"Provided parental consent obtained" |

Based on Table 5.3, the majority of the health practitioners, 19/28 (68%) who responded “no” for the proposed trial have concerns over the use of pharmacological management in the study due to the documented side effects of anti-reflux medications as well as the lack of use of medications in their current practice. In addition, 3/28 (11%) prefer other ways of conducting the trial in terms of study design as well as subjects grouping, while 6/28 (21%) have other reasons that are relating to the hospital’s consent, parent’s permission and infants’ overall conditions.

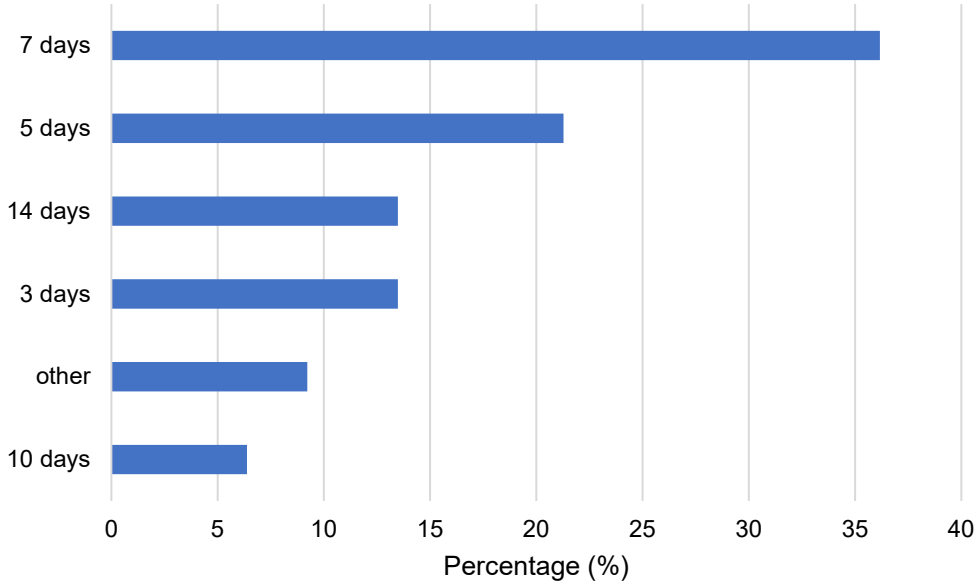



**Figure 5.6: Duration of observation towards non-pharmacological response before starting medications for clinical trial**

Figure 5.6 shows that 51/141(36%) of the health practitioners chose 7 days as the optimal time to wait for a response before starting medications for the proposed clinical trial, while 30/141 (21%) chose 5 days, and 19/141(14%) chose 3 days. 9/141 (6%) and 19/41 (14%) chose longer waiting periods of 10 days and 14 days, respectively.

Other free text answers from 13/141 (9%) responses could be summarised as below:

- Not agreeing with pharmacological management
- Depends on the trial protocol/happy to comply
- Longer than 14 days
- Depends on infants' condition
- Until 38 weeks GA

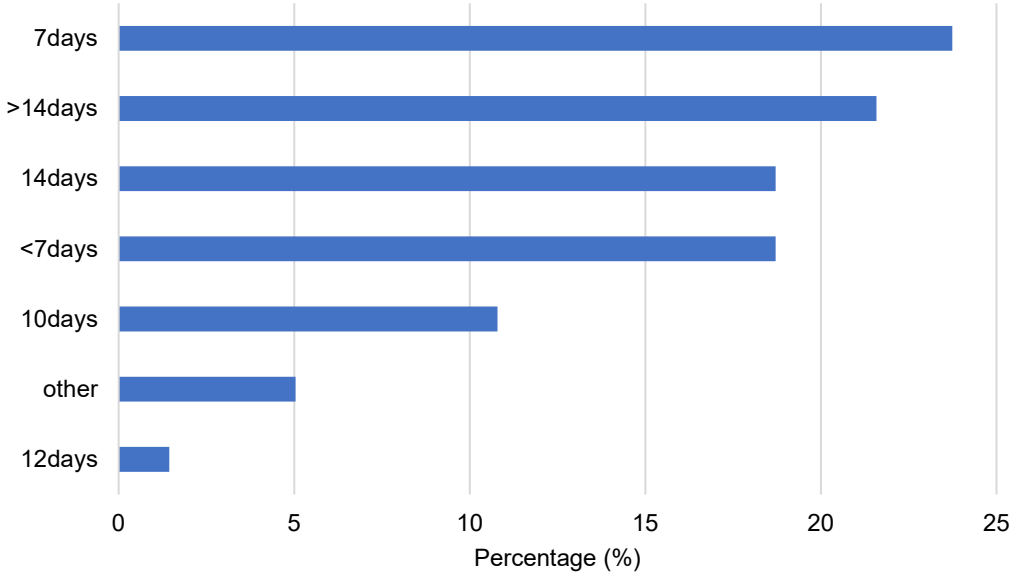



**Figure 5.7: Suggested outcome for reduction of anti-reflux medications' use (days)**

Figure 5.7 shows that 33/139 (24%) of the health practitioners who responded agree for 7 days as the optimal measurable outcome for reduction in medication use for the proposed trial, followed by more than 14 days, 30/139 (22%) and 14 days, 26/139 (19%), while 26/139 (19 %) agree with <7 days.

Free text answers, 7/139 (5%) were summarised as below:

- Prefer clinical outcome such as growth or oxygen dependency

- Disagree on the use medications
- Disagree with the outcome (no reason stated)

**Table 5.4: Summary of other views on management of GORD in preterm infants**

| Themes and subthemes (n) | n(%) | Quotes |
|---|---|---|
| **Use of medications:**<br>**Unsupportive views (7)**<br>**Alternative suggestion of medication use (4)** | 11(26) | "I don't think pharmacologic therapy is overall beneficial, and is probably harmful in potentially increasing NEC, whereas continuous and transpyloric feeds are benign and seem to help protect the lungs."<br>"EES doesn't work before 32 weeks due to lack of motilin receptors. Treat until around 34 weeks usually, not based on actual weeks but age."<br>"I view GOR as physiological in preterm and by default try to avoid medication" |
| **Non-pharmacological strategies:**<br>**Gradual feeding (1)**<br>**Positioning (1)** | 2(5) | "I dislike forcing large volumes on preterm babies, I would like to see a more gradual increase, as I believe they can go on to develop oral feeding phobias."<br>"Sometimes sitting upright for 20 mins after a feed helps" |
| **Other issues related to GORD:**<br>**Causes of GORD (3)**<br>**Diagnostic test used (1)**<br>**Overdiagnoses/overtreated (3)**<br>**Unclear definition of GORD (2)**<br>**Undertreated (1)**<br>**Do not treat/self-resolved (2)**<br>**Distressing to parents (2)** | 14(33) | "Usually it is a challenge to differentiate GOR and GORD"<br>"Most of cases are transient. And resolve prior to discharge"<br>"I think we underestimate the impact of this on families of these babies and the mixed practice and variable opinions of clinicians can be very hard for parents." |
| **Questions/suggestion proposed trial**<br>**Age of enrolment (2)**<br>**Clinical condition of infants (1)**<br>**Primary outcome (2)**<br>**Disagree on medication use (1)**<br>**Ethics with medication randomisation (2)** | 8(19) | "Unclear from questions if infants would have to reach a certain CGA prior to enrolment"<br>"Would be helpful to have the >32 weeks babies looked at as well<br>I think that this trial needs to be able to assess adverse events as endpoints with good power given the well described associations with ranitidine and infection" |

Table 5.4 shows that 11/43 (26%) of the responses were regarding the use of medication as the management strategy for GORD. 2/43 (5%) commented on the use of non-pharmacological strategies such as gradual increase in feeding and positioning that may help in easing the GOR symptoms. 14/43 (33%) of the responses were based on other issues related to GORD such cow milk protein allergy, feeding tubes, rectal enema, diagnostic test used, overdiagnosis as well as underdiagnosis or undertreatment of GORD.

Some also commented on how GORD should not be treated as it is a self-resolving condition, while others commented on parental concerns over this condition. Lastly, 8/43(19%) of responses were comments and suggestions regarding the proposed trial such as age for the enrolment into the study, suggestion on other primary outcome of the study (i.e. adverse events), disagreement on the use of medications in the study as well as comments on possible ethical issues related to randomisation of medication in the proposed study. Miscellaneous/unrelated responses were not included in the analysis, 8/43 (19%).

### 5.4.6 Objective 4: What are the parents' perspectives of the use of pharmacological and non-pharmacological approach in the initial management of GORD for the preterm infants and what is their preferred management strategies for their infants?

For this objective, a given scenario of a clinical trial where preterm infants would be randomised into an intervention arm (using initially non-pharmacological strategies to manage GORD) and control group (pharmacological management) was explained to the parents in the questionnaire.

Their views are collected as follow:

a. the use of medications or not using medications as initial management strategy in (Figure 5.8 and Figure 5.9)
b. preference of treatment for their infants' reflux symptoms (Figure 5.10) and the reasons on why they preferred the use of medication or not using medications as their infants' initial treatment (Table 5.5 and Table 5.6)
c. the parents' view on the computer chosen treatment (Figure 5.11)

Figure 5.8 and Figure 5.9 below show the scale from 0-10 on parent's views on whether medications are given or not given as the first approach for reflux symptoms (0=Extremely uncomfortable vs 10=Extremely comfortable).

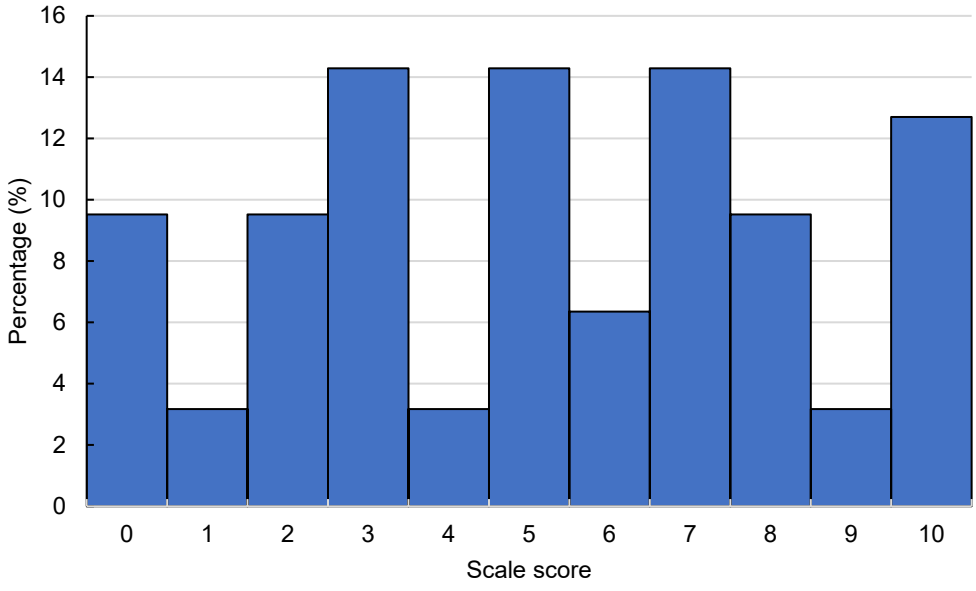



**Figure 5.8: Parents' views on 'given medications as first approach'**

Figure 5.8 shows that the median (IQR, range) scores were 5 (3-5, 0-10) with the highest numbers, 9/63 (14%) responses for scores of 3,5, and 7.

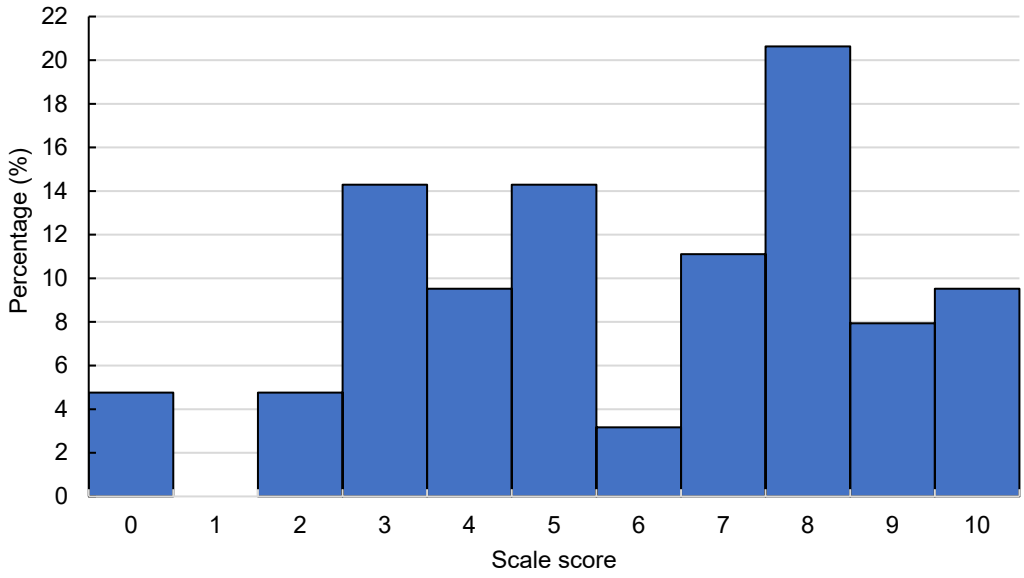



**Figure 5.9: Parents' views on 'not given medication as first approach'**

Figure 5.9 shows that the highest percentage of parents' views with 13/63 (21%) are scored on scale 8, while no one scored on the scale of 1. The median (IQR, range) score is 6 (4-8, 0-10).

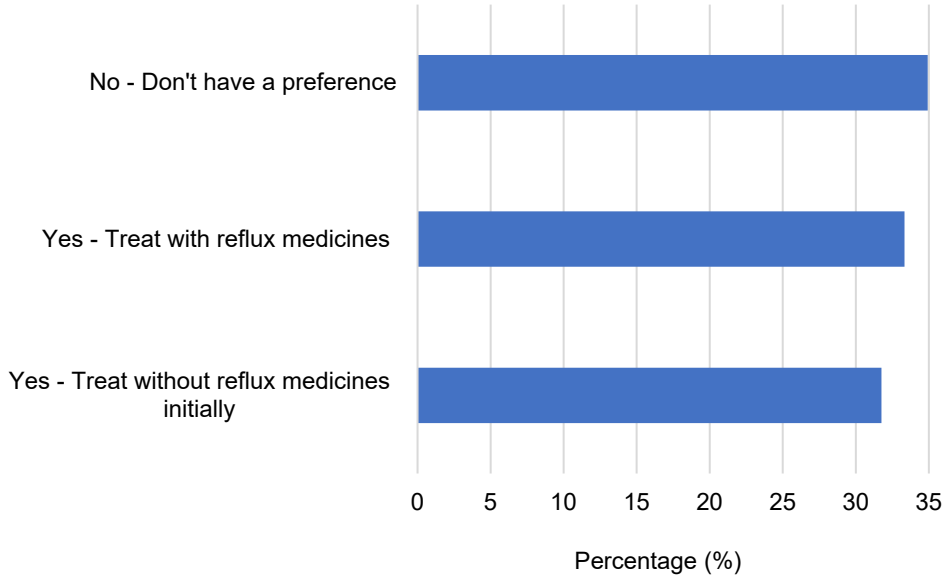



**Figure 5.10: Parents' preferences on types of treatment in managing infants' reflux symptoms**

Figure 5.10 shows that the highest percentage of the parents (22/63 (35%)) do not have any preferences on treatment for managing infants' reflux symptoms, while 21/63 (33%) preferred treatment with anti-reflux medications and 20/63 (32%) preferred not to treat with medications as first treatment approach.

For questions that followed on the reasons why the parents preferred their infants to be treated or not to be treated with anti-reflux medications, Table 5.5 shows responses from 20/21 (95%) parents who preferred initial treatment with anti-reflux medications while Table 5.6 shows responses from all 20 parents who preferred initial treatment without anti-reflux medications.

**Table 5.5: Parents' responses on clinical trial of treatment of GORD in preterm infants - reasons on preferring initial treatment with medications**

| Themes | n(%) | Quotes |
|---|---|---|
| **Confident that it works** | 16(80) | "They have been designed to help with reflux so I would like them to be used. I would not want my baby to suffer for longer than they have to."<br>"Because not doing so led to unwarranted test and invasive procedures only for a different doctor to take one look and provide medicine that aided instantly"<br>"Unless fully explained to me, I would always assume that treating a condition with medicine would be the most effective way forward."<br>"Because it was an immediate problem that needed a quick fix. Was happy to look at alternative treatments once her breathing had stabilised." |
| **Past experiences** | 4(20) | "They worked for my son who had symptoms which lasted a number of weeks before diagnosis.."<br>"My son had reflux and it was awful. As soon as he started medication, he was happier, and we all settled."<br>"Our LG had lots of bradycardia and sleep apnoea due to reflux which subsided dramatically when finally put on medication." |

Table 5.5 shows that the majority of parents, 16/20 (80%) who responded to medications as preferred approach for the initial treatment for their infants believed that the medications could be a “quick fix”, “aid the symptoms instantly” and they also concern that their infants could be suffering if not given medications. The remaining 4/20 (20%) of the parents preferred the medication use due to their positive past experiences with their infants who have had it.

**Table 5.6: Parents' responses on clinical trial of treatment of GORD in preterm infants - reasons for preferring initial treatment without medications**

| Themes | n(%) | Quotes |
|---|---|---|
| **Concern for side effects of medication** | 9(45) | “Because of concern of over treatment, and a desire to avoid any potential long-term effects”<br>“Avoidance of potential side effects”<br>“Because they are so small and usually any kind of antacid etc causes issues with nutrient absorption and also might cause needless dependency on other wise unnecessary drugs” |
| **Consider trying non-medicines approach** | 8(40) | “I would tend to prefer non-medicinal intervention for this problem.”<br>“To see if it can be rectified without medication first”<br>“I think it makes sense to attempt to avoid medications first if it is possible. You are in a safe setting with medical professionals around you. It’s the best time to try the non-medicated route” |
| **Past experience** | 3(15) | “This was my second child suffering reflux. The first was on multiple different medicines and his did not improve with any of them. It gradually improved as he aged. With my new baby I didn’t want him pumped full of different medicines…”<br>“We were prescribed omeprazole, ranitidine and Gaviscon. We chose not to start anything apart from Gaviscon as we felt our son had had so many drugs already administered to him that reflux was the least of his problems. We persevered and have up on the Gaviscon in the end and he eventually grew out of it.”<br>“I don’t feel like the reflux meds did much to help our son, if anything I feel the ranitidine made him worse” |

Table 5.6 shows that 9/20 (45%) of parents who preferred not to use medications as the initial treatment for their infants were concerned over the potential side effects of the medications. 8/20 (40%) of the parents were receptive to try non-pharmacological approach first, while another 3/20 (15%) chose this option due to past experiences of medications use with their infants.

Lastly, when the parents were asked to give a scale score from 0-10 (0=Extremely uncomfortable vs 10=Extremely comfortable) of their views on computer chosen treatment, the results are shown in Figure 5.11 (n=63).

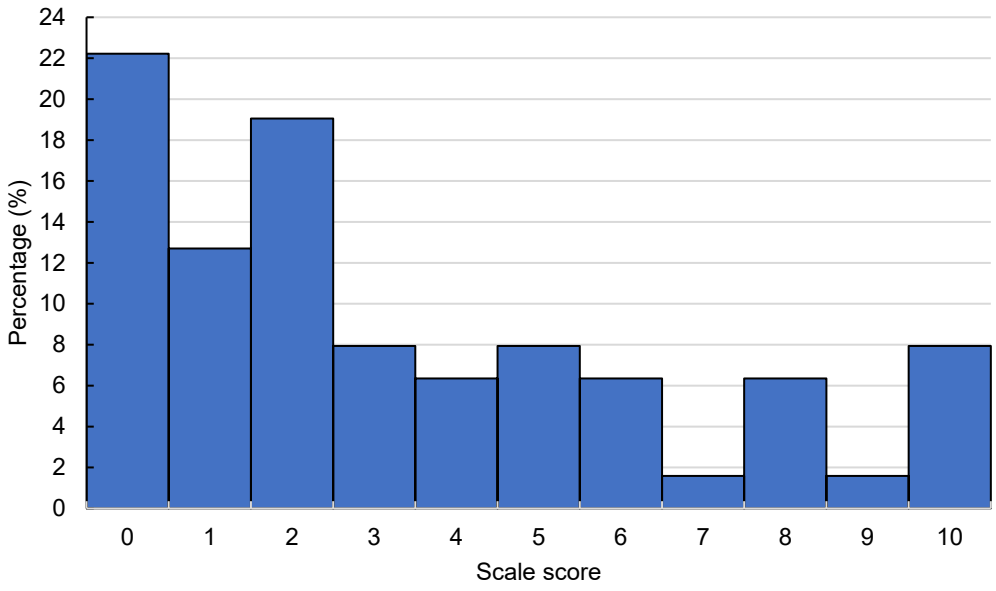



**Figure 5.11: Parents' views of the computer chosen treatment (0=Extremely uncomfortable vs 10=Extremely comfortable)**

Figure 5.11 shows that the highest percentage at 14/63 (22%) of parents scored the scale at 0 (extremely uncomfortable), followed by scale of 2, 12/63 (19%) on their views for computer chosen treatment. The lowest percentage were at scale 7 and 9 (1/63, 2%). Median (IQR, range) score for the scale is 2 (1-5, 0-10).

### 5.4.7 Objective 5: What is the parents' perspective on a proposed trial randomising infant into pharmacological or non-pharmacological management for GORD and what are their views on infants' care and important outcome measures for the trial?

For this objective, based on the same given scenario of a clinical trial as in previous objective, parents' views were collected as follows:

a) the participation into the proposed study and data collection process (Figure 5.12)
b) infants' care and important outcome measures of the proposed study (Figure 5.13 and Figure 5.14)
c) other comments on the proposed study or management of GORD in general (Table 5.7).

In general, with regards to the participation in the proposed clinical trial, 52/63 (83%) of the parents agreed to take part while 11/63 (18%) did not agree in taking part. However, for the data collection process during hospital admission and after discharge, 62/63 (98%) of the parents agreed while only 1/63 (2%) parent declined.

While there were 11/63 (18%) parents answered that they would not agree to participate in previous question, 17/63 (27%) responded on their views for not considering in participating in the trial in this following question as shown in Figure 5.12.

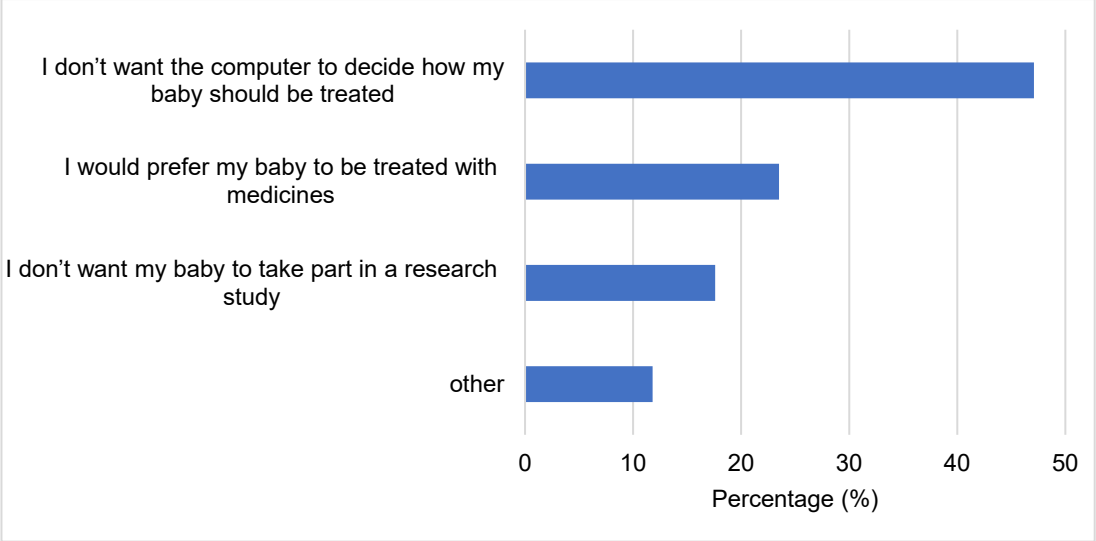


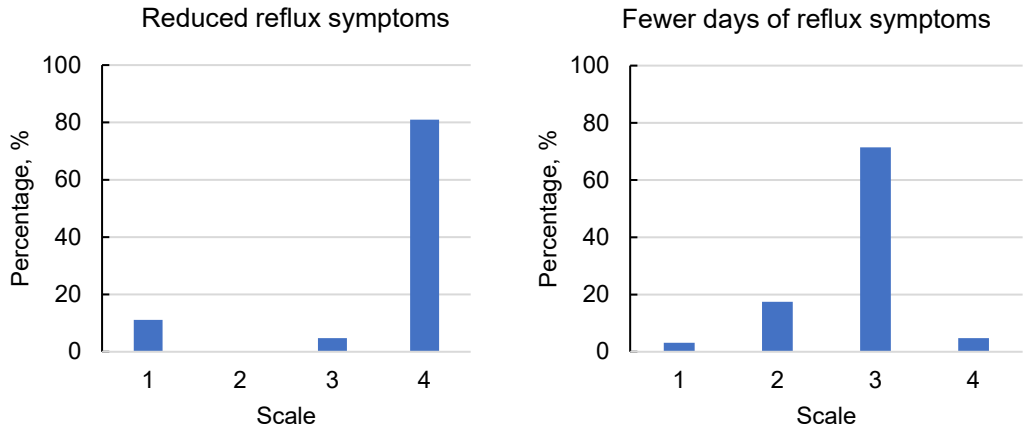

**Figure 5.12: Parents' view on not participating in the proposed study**

Figure 5.12 shows that 8/17 (47%) of the parents who responded answered that they would not want the computer to decide their infants' treatment, 4/17 (24%) preferred their infants to be treated with medications, and 3/17 (18%) stated that they would not want to take part in a research study. The remaining respondents who answered 'others', 2/17 (12%) are quoted as follow:

- "I would want to discuss symptoms with a doctor"
- "Her reflux is under control and I don't want it to flare up"

To investigate further into parents' views if they agree to participate in the proposed trial, their views concerning infants' care if they do have twin infants with reflux symptoms were asked. From 51 parents who responded, 27/51 (53%) preferred both infants to be cared in the same way (same intervention), 19/51 (37%) did not have any preference while 5/51(10%) preferred both infants to be cared differently.

Figure 5.12 and Figure 5.13 show parents' views on their preferred outcomes measures for the proposed clinical trial based on the i) reflux symptoms, and ii) anti-reflux medications use.

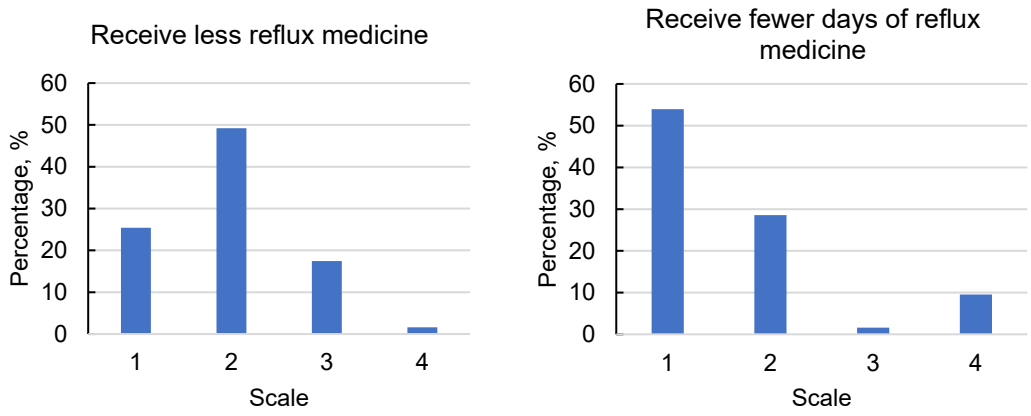



a) Left: Reduced reflux symptoms

b) Right: Fewer days of reflux symptoms

**Figure 5.13: Parents' views on the outcome measures (reflux symptoms) for the proposed study (1 being least important, 4 being most important)**

When asked about outcome measures in terms of reflux symptoms for the trial, 51/63 (81%) of the parents chose scale of 4 for "reduced reflux symptoms" as the outcome measure (median (IQR, range) scale of 4 (4-1, 1-4)). For "fewer days of reflux symptoms, highest percentage of parents (45/63 (71%)) chose scale of 3 with median (IQR, range) scale of 3 (3-3, 1-4).




a) Left: Receive less anti-reflux medications b) Right: Receive fewer days of anti-reflux medications

**Figure 5.14: Parents' view on the outcome measures (anti-reflux medication) for the proposed study (1 being least important, 4 being most important)**

When asked about outcome measures in terms of anti-reflux medications use for the trial, for the outcome “receive less anti-reflux medications”, the majority of parents (31/63 (49%)) chose scale of 2, median (IQR, range) of 2 (1-2, 1-4), while for “receive fewer days of anti-reflux medications”, the highest proportion of parents chose scale of 1 with 34/63 (54%), median (IQR, range) scale of 1 (1-2, 1-4).

Therefore, among the four outcomes, the highest proportion of parents chose “reduced reflux symptoms” as the most important outcome and “receive fewer days of anti-reflux medications” as the least important outcome for the proposed trial.

For other suggested outcomes, free text responses, 7/63 (11%) are summarised as follow:

- Increase use of other strategies other than medicines for treatment such as natural remedies
- Non-related to outcome measures

Lastly, Table 5.7 shows analyses of parents’ views on the proposed study or management of GORD in preterm infants in general.

**Table 5.7: Parents' comments on proposed trial/GORD management**

| Themes | n (%) | Quotes |
|---|---|---|
| **Parental support with management of GORD** | 4(21) | "Our anxiety over our daughter not keeping milk down and not putting on weight was extreme, it didn't last forever but you will need to be extra reassuring that babies are being carefully monitored"<br>"Please, please, please listen to the parents"<br>"Yes - please consider what happens in the community when babies are diagnosed after discharge……. to demonstrate ongoing interest in outcomes would be nice for parents who can feel that no one cares for them once they leave the unit. Reflux is exhausting." |
| **Questions/suggestions on proposed trial** | 4(21) | "We only had problems after we were discharged from hospital when milk feeds increased. Will both breastfed and formula feed babies be included and analysed separately?"<br>"So if a baby has silent reflux and aspirated on it what would demerit them more medication or using the technique advised above"<br>"Are there sufficient neonatal staffing levels to allow smaller but more frequent feeds for all affected babies?" |
| **Experience with GORD/medication use** | 11(58) | "My baby had reflux. She is three and still has reflux. Solutions given to us didn't work and actually made things worse. They increased feed volume and did not refer to consultant until one year after discharge from NICU."<br>"I wish these options were available to us. My son is now 19mths and is still on omeprazole for reflux. …… It does concern me he is still on medicine now, but it does help his symptoms."<br>"My baby had reflux n I changed my diet a little as I was breastfeeding. He had fewer vomiting episodes. Reflux completely disappeared when he was 4 months. Longer burping can help babies from reflux too" |

Based on Table 5.7, 4/19 (21%) of parents commented on the need for parental support in the management of GORD for their infants during admission and after discharge, 4/19 (21%) had questions on the proposed trial such as the adequacy of staff (staff numbers) for infants' intervention as well as infants' care, while majority

of parents 11/19 (58%) responded by sharing their experiences dealing with their infants' reflux or the use of medications for the treatment.

## 5.5 DISCUSSION

This survey provides health practitioners' self-reported practices and perspectives on the management of GORD among preterm infants in neonatal units as well as parents' perspectives on the treatment of GORD and a proposed clinical trial in this area. The majority (62%) of health professionals in this survey consisted of Consultant Neonatologist/Paediatricians and PostgraduateTrainees in Neonatology/Paediatrics while others were nurses, nurse practitioners and allied health practitioners. Participants were from various countries including the USA, Turkey, Denmark, Austria, Oman, Australia, Sweden, Saudi Arabia, Spain, Chile, and Brazil. From participants who provided their contact details (n=72), 76% were from UK units while 24% were from other countries.

The management strategies reported in this study are based on health practitioners' self-reported practices. It is known that there are a lot of uncertainties in the diagnosis of GORD in neonatal units which may be correlated to a lack of understanding of the proper way to treat it, as well as difficulties in differentiating physiological GOR from pathological GORD (212). In addition, diagnosis and management approaches are usually influenced by GORD-perceived symptoms observed in the infants, parents' perception, respective neonatal unit's protocol or system as well as the health professional's decision which is usually based on the attending clinician's perception of GORD (179). The combinations of these factors may lead to both over- and under- diagnosis and treatment of GORD in preterm infants.

### 5.5.1 Diagnostic criteria and tests used to establish a GORD diagnosis

From the survey, the most common signs/symptoms perceived to be related to GORD were desaturations that occur during or after feeds, back arching or head extension, and apnoea occurring during/after feeds. In the guideline provided by the NASPGHAN-ESPGHAN (2018)(171), a list of 22 symptoms and signs that might be indicative of GORD for infants and children was compiled, together with 16 gastrointestinal and systemic manifestations, that might be the 'red flags' suggesting possible other illness apart from GORD in the infant presenting with regurgitation and/or vomiting symptoms. This guide however is not well-defined in its applicability to infants in the neonatal unit or preterm infants, so the reliability of these symptoms as an indication of GORD is not clear.

From the survey's results, only apnoea was listed as one of the signs that might be associated with GORD in infants as per the guideline. In a study of preterm infants who were referred for multichannel intraluminal impedance (MII) and pH monitoring tests based on cardiorespiratory monitoring study, more GOR events were detected to have occurred after a feed than before feed, but the rates of apnoea, bradycardia and desaturations were not changed (392). Apnoea was however shown in another study (393) to have a temporal relationship with weakly acidic reflux events. Apnoea was also chosen as one of the common signs used in diagnosing GORD by neonatologists in a UK survey study (241). For desaturations, the health practitioners' opinion in this survey might be influenced by studies in adult populations that showed a high occurrence of desaturation associated with GOR as detected with MII-pH testing (394,395). These studies however were mostly performed in patients with primarily respiratory symptoms and might not apply to other patients'/age group.

In addition, other symptoms commonly associated with GORD such as back-arching occur frequently even in healthy infants and there is no evidence that these symptoms are temporally associated with GOR events (171).

From this survey, the majority of the health practitioners reported that they do not use any test to investigate possible GORD and base their diagnosis on clinical assessments. This is followed in frequency by the use of pharmacological trials and also non-pharmacological management, both without any tests performed.

Consistently, a study involving European countries (396) found that almost half of the paediatricians used clinical symptoms and physical examination for a diagnosis of GORD without further investigations regardless of patients' age and this was also shown in other studies in France (397) and USA (398). This is parallel with the 2018 NASPGHAN-ESPGHAN and 2015 NICE recommendations that in the case of an uncomplicated infant with GOR, a thorough assessment of medical history and physical examination should suffice in establishing a clinical diagnosis after excluding other possible diagnoses as stated in the current guidelines (171,212).

Similar findings were seen in a survey study in the UK in 2004 (241) in which approximately 40% of respondents stated that they use clinical criteria alone for diagnosing and a higher proportion (50%) used a combination of clinical features, investigations and trials of therapy. However, in a recent study in the UK in 2018 (242), a pharmacological trial of therapy was then shown as the most commonly used diagnostic method in neonatal units in all infants, followed by tests such as pH studies. On the contrary, a study among paediatric specialists in the US (399) showed that neonatologists, amongst other specialists, were least likely to report that a trial of therapy would be useful for diagnosing GORD, and believed that neither H2RA nor PPIs are safe or effective.

However, the method of a trial of therapy using anti-reflux medications as diagnostic testing for GORD is inconclusive for preterm infants. This is probably due to the unclear symptoms associated with GOR in preterm infants and the possibility of symptom improvements due to increasing age or maturity rather than as a response to the medication. The survey results also showed that the majority of health practitioners who chose trial of therapy would prescribe the medication for only one week or less than one week. This may not be long enough. The 2015 NICE guideline (212) advised that a 4-week trial of a PPI or H2RA could be an option for patients who are unable to tell about their symptoms (i.e. infants and young children, and those with neurodisability/communication difficulties) who have overt regurgitation with one or more of the following conditions: i) unexplained feeding difficulties (for example, refusing feeds, gagging or choking) ii) distressing behaviour, or iii) faltering growth.

This is also supported by the 2018 NASPGHAN-ESPGHAN guideline (171) which stated that a “short” trial of a PPI is not recommended as a diagnostic test for infants, which was also similarly indicated in the previous version of the guideline in 2009 (387). This was in line with the results from five RCTs of using PPIs in preterm and full-term infants for a treatment period range of 2 – 4 weeks treatment period that showed no symptom reduction over placebo regardless the length of the trial (198). Therefore, similar to NICE, this guideline suggests that when an infant is presented with frequent regurgitation and/or vomiting, a 4-8 week trial of acid suppression could be considered if symptoms have not improved with non-pharmacological approaches and referral to paediatric GI is not possible (171).

In this survey, amongst those who do use diagnostic tests, pH monitoring was more commonly chosen as diagnosis test as compared to upper GI contrast and MII monitoring as also shown in other studies (241,242). However, it might not be a reliable method to diagnose GORD for preterm infants due to their frequent milk

feeding which changes their gastric pH to be more alkaline (>4). Some studies also showed that abnormal pH monitoring does not correlate well with the severity of symptoms (172,197).

Lack of access to pH or MII investigation, a weak association between symptoms and the results of investigations as well as the difficulties encountered in the interpretation of the result could be the reasons for its lack of use (242). Although an earlier study in the UK (241) showed that pH monitoring was available in almost all units, only 32% of respondents said they used it regularly in suspected cases. The ESPGHAN-NASPGHAN guideline also does not suggest the use of pH-monitoring or pH-MII for the diagnosis of GORD in infants and children due to lack of evidence (171).

### 5.5.2 Main management strategies used in preterm infants with GORD in neonatal units

For the treatment or management of GORD, the majority of the health practitioners reported that they first try non-pharmacological strategies followed by prescribing medications or they only use non-pharmacological strategies. Reducing the feeding volume by increasing feeds frequency were reported as the main non-pharmacological strategy in this survey, followed by the use of positioning as head-up angle and head-up angle with an upright position. The choice of non-pharmacological strategies was in parallel with the 2018 NASPGHAN-ESPGHAN recommendation that the initial management in the suspected cases should be conservative and tried in a stepwise manner (171). This usually includes changes in feeding practices and/or parental education and counselling. However, there is a lack of evidence available for preterm infants in determining which strategies are the most effective.

The use of smaller, but more frequent, feeds as mostly chosen by survey respondents has been found to decrease GOR events in studies (187,188). However, it may also lead to more frequent acidic reflux episodes as well as some reported increase in the incidence of gastrointestinal disturbance (189). No studies, however, have shown a strong relationship between the volume of milk ingestion with the amount or episodes of regurgitation. In addition, using strategies such as continuous feeding may compromise the nutrient composition of expressed breast milk especially the energy content due to possible fat loss (188). Reducing feed volumes compromises nutrient intake and may lead to a longer time taken to reach full enteral feeding and will affect infants' weight gain and growth. Therefore, cautious feeding is suggested by avoiding overfeeding and considering appropriate feeding frequency and volume according to age and weight to ensure an adequate and appropriate total daily amount of milk for the infant (171).

Another recommendation in terms of feeding intervention is to change infant's milk to elemental or extensively hydrolysed protein formulas (eHPF), as studies showed that the use of an eHPF improved GOR symptoms in infants with suspected GOR (190), while in preterm infants, it significantly reduced the number of GORs detected by pH monitoring ($p= 0.036$) and also the reflux index ($p = 0.044$) when compared to the standard preterm formula (211). However, this is not a better option for breast-fed infants as it might encourage the switching to formula feeding.

Body positioning by the way of head elevation or using head-up slope is a common practice (241). However, studies in term and older infants showed that head elevation is ineffective in reducing acid GOR either in prone or supine positions (400,401). Placing infants in the left lateral versus right lateral position after feeding and in prone versus supine position however, was shown to reduce TLESRs and reflux episodes in preterm infants (187,193). However, many guidelines strongly

advise that infants with GOR should lie in the supine position, except for those exceptional cases where the infants' risk of death from GOR is greater than the risk of Sudden Infant Death Syndrome (SIDS) (195).

### 5.5.3 The use of pharmacological intervention in the initial management of GORD in neonatal units

In this study, significantly fewer health professionals reported using pharmacological intervention as the main strategy in managing GORD, as compared to those who used non-pharmacological management. The majority of the health practitioners who use medications chose PPI to manage GORD, followed by feed thickener with antacid such as Gaviscon, and only a smaller proportion of them selected H2RA and prokinetics. Over a fifth of respondents said they continued the medications' prescriptions after discharge, until the next follow-up. In comparison, the majority of respondents of the 2018 UK study (242) used Gaviscon, followed by H2RA (Ranitidine), feed thickeners, PPI, and prokinetics (domperidone and erythromycin). This was similar to the UK survey in 2004 (241) which involved preterm infants only in which H2RA and feed thickeners were mostly used in almost all units, with Carobel instead of Gaviscon as the most frequently used feed thickener. In addition, my retrospective cohort study in Chapter 4 using the national database (NNRD) also presented that majority of infants in England and Wales who received any types of anti-reflux medications from 2010-2017 received Gaviscon (57%), followed by H2RA (52%), prokinetics (47%) and PPI (14%).

This contradicted with higher self-reported use of PPI in this survey, as also opposed to previous UK surveys. This might be because the current survey involved health professionals in other countries' neonatal units as well, and it might

be more comparable to studies involving European units in 2014 (396) where the majority chose PPI as the preferred treatment of GORD, similar to a US study (398).

In the current ESPGHAN-NASPGHAN and NICE guideline, it is stated that PPIs or H2RA should not be used in treating visible regurgitation in infants that occurs as an isolated symptom in a healthy infant. The former guideline also recommended PPI as first-line treatment of reflux-related erosive esophagitis in infants with GORD, and the choice of PPIs or H2RA depends on accessibility and cost, as no available evidence supports the superiority of PPI or H2RA over another.

However, as demonstrated in this study, there was much lower self-reported use of H2RA (c.20%) as compared to PPI (c.60%) which could also be possibly due to increasing evidence of the association between necrotising enterocolitis (NEC) and H2RA use in infants (200,201,203,205). The use of Gaviscon was also higher than earlier studies, possibly due to the lack of reported side effects as compared to H2RA and prokinetics (243). Interestingly, although the use of prokinetics such as metoclopramide, domperidone and erythromycin have been strongly warned in many countries due to documented adverse effects such as cardiac arrhythmias (244) and hypertrophic pyloric stenosis (245), c.16% of the health practitioners respondents in this study reported to still use them. The use of these agents was shown to be higher ( c.28%) in previous study (242).

Finally, in the scenario of a clinical trial given in this study, the majority of the health practitioners would consider participating in the study. A higher number of them chose 7 days as waiting time for response (in using non-pharmacological strategies) before initiating medications and 7 days as the optimal measurable outcome for a reduction in medication use.

This probably showed that a week of non-pharmacological trial was mostly chosen based on their clinical experience which was deemed sufficient to observe any

symptoms relief without the use of medications. Interestingly, a smaller number of health practitioners chose 14 days (the longest duration) for the observation period – which could also be suggestive of their intended need or usual practice in starting medications for suspected GORD cases in their unit. However, as suggested in the current guideline, for each of the non-pharmacologic strategies (i.e. use of thickener, feeding modifications or use of extensively hydrolysed formula or amino acid-based formula), a minimum of a 2-week trial is advocated to assess for any symptoms improvement before other strategies should be started (171).

Among those who would not agree to participating in the proposed trial, the majority of them have stated concerns over the use of medications in the proposed trial due to the reported side effects as well as lack of medication use in their respective units' practice. This would possibly suggest that the use of anti-reflux medications and their side effects have been increasingly acknowledged among these health practitioners.

As a summary on the management of GORD among preterm infants from health practitioners' perspectives, 26% of the respondents in this study showed various unsupported opinions on the use of medications for GORD in preterm infants while 33% gave their views on multiple issues regarding GORD management in which problems such as difficulty to differentiate between GOR and GORD as well as problems of overdiagnoses and overtreatment were raised. This survey, therefore, showed variability in understanding, clinical practices and also high awareness in the safety aspects of anti-reflux medications use in preterm infants from the health practitioners' perspectives.

### 5.5.4 Parents' perspectives on the management of GORD in preterm infants

In this survey, parents' perspectives were collected as a response to the given scenario of a clinical trial where preterm infants would be randomised into an intervention arm (using initially non-pharmacological strategies to manage GOR) and control group (pharmacological management).

On the scale of 0-10 (0=Extremely uncomfortable vs 10=Extremely comfortable), a median score of 5 was received for parents' view on 'given medications as first approach', but a higher score of 8 was received for 'not give medications as first approach'. This difference in scoring might show that parents have a good understanding of the importance of starting the management of GORD in preterm infants using a non-pharmacological strategy. It might also indicate that they were also well-aware of the documented side effects of certain medications on preterm infants and have conflicting concerns about it as also implied in the use of medication for other illnesses. This contradicts a study that has shown that when infants were labelled to have GORD as a diagnosis, parents are more likely to be interested in using medications for their infants, even if they are known to be ineffective (390). It could be that all parents in this survey who had the experience of having preterm infants in the neonatal unit possess more understanding that these infants are more fragile and clinically vulnerable which makes them more cautious of medications received in the unit. It might also be that the initial scenario given in the proposed trial provides them with a different opinion or bias on the use of medications for GORD in preterm infants.

This could be seen in the next question regarding preference on reflux symptoms' management, where the proportions of parents who do and do not have any preferences as well as those who prefer treatment without reflux medications were very similar (35% vs 33% vs 32%).

The majority of the parents who preferred medications as initial treatment mostly believed that these medications are effective and could instantly fix their infants' symptoms. This was possibly due to their own opinion or biased experience that there should be medication use for every clinical condition, the experience of using anti-reflux medications in self or other children, or their concerns that not choosing medications might bring more harm to their vulnerable infants. As expected, those who do not prefer the use of medications were concerned about side effects as well as their willingness to try non-pharmacological strategies first. This could also show some bias in the study in which parents might already have the impression of the superiority of one approach over another from the scenario given on the proposed trial, or these parents were already well-equipped with the knowledge of these medications.

However, when asked about their view on computer-chosen treatment for their infants, the highest proportion of parents scored the scale at 0 (extremely uncomfortable). This clearly showed that although the proportion of parents who do or do not have preferences on the initial treatment were almost the same, they strongly showed that they are not comfortable with randomly selected treatment by a computer. This indirectly suggests that health practitioners' clinical decision on determining treatment for their infants was more reassuring for them. Other than this strong disapproval of computer-selected treatment, almost >80% of parents would agree to participate in the trial and to conform to the data collection process indicated during admission and after discharge.

In considering the outcome measures for the trial, with 1 being least important and 4 being most important, the largest number of parents chose "reduced reflux symptoms" as the most important outcome and "receive fewer days of anti-reflux medications" as the least important outcome for the proposed trial. This possibly showed that the most troubling part of managing infants' GORD for parents is the

occurrence of reflux symptoms. They also had some views that less use of medications would be beneficial.

## 5.6 CONCLUSION

It is known that establishing a GORD diagnosis and deciding which strategy to use in managing GORD among preterm infants is challenging. Clinical features as commonly seen in older children and adults are non-specific and not similarly evident in preterm infants. In addition, many signs and symptoms may be confused with a number of other prematurity-related illnesses. Additionally, recommendations and guidelines for the management of GORD in infants changed over the years as new evidence on lack of effectiveness and side effects of medications emerged. This also led to the unclear, conflicting and inconclusive suggestion for clinical practice, specifically for preterm infants.

Therefore, in this survey, current perspectives on the management of GORD in preterm infants are presented from two points of view, health practitioners and parents of preterm infants. This study showed that, among health practitioners, there is still variability in deciding on signs and symptoms which could be related to GORD in preterm infants. However, self-reported strategies used in their clinical practice are quite consistent as the majority reported to attempt a trial of non-pharmacological approaches followed by pharmacological management combined with non-pharmacological approaches whilst many fewer respondents chose pharmacological management as their main strategy. Only a few respondents noted that GORD is a self-resolving condition. In terms of the pharmacological therapy chosen, PPI and feed thickener with antacid (i.e. Gaviscon) were the two commonly used therapies preferred and prokinetics were the least used.

As for parents' perspective on the management of GORD for preterm infants, this survey generally showed that parents have some understanding of the use of non-pharmacological strategies in treatment for GORD. However, further information and reassurance are needed for increasing awareness about the lack of evidence to support the use of anti-reflux medications and why using medications should not be viewed as the "easy and quick solution" in managing GORD in these infants.

Despite many studies that showed that overtreatment and overprescribing of anti-reflux medications occur in many neonatal units, clear, concise and consistent guidance are not available specifically for preterm infants and hence such overtreatment is difficult to tackle. It is crucial that both practitioners and parents understand and are able to differentiate between normal, physiological GOR and GORD. Both parties also need to understand the limitation of pharmacological therapy and the risk of associated adverse effects and consider if it is necessary to prescribe. Effective communication and continuous support between the health practitioners and parents on the best available management for symptoms' relief of GOR or GORD that could be attempted for infants must be maintained at all times in the neonatal unit and after discharge.

## 5.7 STRENGTHS AND LIMITATIONS

To my knowledge, this survey which was undertaken as a patient and public involvement activity (PPI) is the first to capture parents of preterm infants' perspective on the management in GORD in the neonatal unit which explore what outcomes matters the most to parents following the GORD treatment. The involvement of 154 health practitioners and 63 parents in this study presented a good sample size for our analysis. As this study was disseminated through an email list as well as social media, Twitter ™ (http://www.twitter. com), this enabled the survey to reach health practitioner participants from all over the world including the

USA, Turkey, Denmark, Austria, Oman, Australia, Sweden, Saudi Arabia, Spain, Chile, and Brazil. This has been shown in many studies that social media delivers an efficient and cost-effective space for recruiting hard-to-reach populations for survey research such as this cohort and offers targeting capabilities that assist in attracting participants' interest and recruitment (402).

These features help in reducing the time and resources required to conduct such studies even when we are in the middle of a pandemic. This was also applicable in reaching parents of preterm infants as the tweet was shared widely by specified preterm infants-related organisations and groups such as Bliss Baby Charity, Neomates and NCT Charity leading to high participation in this study.

However, I am also aware of the limitation of this study. Health practitioners participated from various parts of the world and we could identify the country only where an email address or specific information was volunteered by the participant as the survey was otherwise anonymous. I was not able to draw a comprehensive picture of the trends of medications or management strategies used inclusively based on certain locations or regions because of the nonhomogeneous participation of countries. This also means that I could not do separate analysis of the varied practice based on the demographic or nationalities due to inadequate information. Furthermore, this survey captured the self-reported beliefs of the practitioners. Such responses may represent their actual practice or just their intended practice. The possibility of response or non-response bias might also exist in which it is possible that those with more interest in GORD would have been more likely to complete the study questionnaire. Therefore, a bias could have been presented by the inclusion of well-informed health practitioners. The same also applies to the participation of parents in the survey which were largely recruited from social media platform of organisations such Bliss and Neomates in which there is a possibility that these

parents come from a higher education or have more interest/knowledge on the GORD treatment, hence there could be bias in the responses collected.

Nevertheless, the findings of this survey suggest that health practitioners, in general, have strong views on the management of GORD in preterm infants. Some are aware of the current guidelines especially in the use of anti-reflux medications, concerns associated with their use and non-pharmacological strategies that can be attempted. Parents' views also showed some strong opinions in types of therapy preferred for GORD, but there is a definite need for better communication of evidence-based information in many sources, either from the clinicians, health information websites or even social media. Any proposed clinical trial in determining the effectiveness of non-pharmacological strategy versus pharmacological strategies in managing GORD in preterm infants should be meticulously planned with consideration of parents' concerns and standpoints.

# CHAPTER 6: CONCLUSION

This thesis was commenced to describe two significant topics within the care of newborn infants in neonatal units. Firstly, in the nutritional care of preterm infants in neonatal units, a prospective study on nutritional practices and growth outcomes among preterm infants was performed. This was followed by a more specific study on breast milk feeding in a neonatal unit, focusing on the impact of restrictions during the COVID-19 pandemic on the prevalence of breast milk feeding during admission and at discharge. Secondly, to investigate the prevalence of gastro-oesophageal reflux disease (GORD) and anti-reflux medication use among preterm infants in neonatal units, a retrospective cohort study by using data from NNRD from 2010-2017 was performed, followed by a PPI survey study of health practitioners' and parents' perspectives on the management of GORD and the use of pharmacological therapy versus non-pharmacological therapies.

This chapter summarises the main findings of this thesis and reviews the implications for clinical practice and future research.

## 6.1 SUMMARY OF FINDINGS

### 6.1.1 Study 1: Nutrition and growth of preterm infants in the two neonatal units, in the UK and Malaysia

This study aimed to describe and compare nutritional practices in feeding preterm infants in two neonatal units in Malaysia and the UK and assess the association between feeding practices and growth outcomes at discharge. I showed that there are differences in feeding practices and nutritional intakes of preterm infants

between the two neonatal units and that these impact growth outcomes at discharge. However, different factors could have affected the growth outcome (weight-for-age Z-score, WAZ) of infants between the units at discharge. In the Malaysian unit, when nutritional intakes were generally adequate with improvement in the cumulative nutrient deficits after the first week of life, the longer stay was found to be the only significant factor that affected the growth at discharge. This is, however, predictable considering the higher level of care this unit was providing and this was substantiated by more infants with preterm-related morbidities and more receiving PN compared to the UK unit.

On the contrary, in the UK unit, more nutrition-related factors, specifically protein intakes and protein energy ratio (PER) in the first 4 weeks of life in this cohort positively predicts the weight-for-age Z-score (WAZ) changes at discharge. This is likely reflected in the high cumulative protein deficits shown for the whole hospital stay for most infants. Therefore, I can conclude there were variations in nutritional practices between the two units included in this study. Current nutritional practices often do not meet recommended intakes, especially for protein in preterm infants. In the cohort of preterm infants with different clinical conditions and varying characteristics such as birth weight and GA, early and frequent monitoring and evaluations of nutritional intakes and growth in the neonatal units are necessary to identify the specific needs of these infants, even in the apparently ‘healthy’ infants.

### 6.1.2 Study 2: Impact of COVID-19 on breast milk feeding during admission and at discharge from UK neonatal units

This study aimed to describe the prevalence of breast milk feeding during admission and at discharge among infants admitted to a neonatal unit in England, comparing data before and during the COVID-19 pandemic.  Results showed that there were

fluctuations in the breast milk feeding prevalence at discharge during the early COVID-19 pandemic period as compared to the pre-pandemic period, but this was not significant. There were however natural variations and unexpected fluctuations observed in the prevalence of breastfeeding across the admission periods which make the analysis of the true effects of the COVID-19 pandemic and its restriction in the neonatal unit towards the prevalence of breastfeeding to be challenging. There was also limitation on the use of BadgerNet as the main database as it is prone to data entry error due to inconsistent data entries and missing information. However, the overall prevalence of receiving breast milk at discharge and exclusive breast milk was shown to be much lower than receiving any breast milk during admission and there were generally reductions in odds for all three breastfeeding outcomes in the early, and later phase of COVID-19 as compared to pre-pandemic period, but the differences were not statistically significant in either the unadjusted or adjusted models. This could be due to the small sample size in this study which may not, therefore, be sufficiently powered to detect a difference between the periods. Other factors such as the breastfeeding policies in the study unit which follows the WHO recommendations for continuation of breastfeeding for infants either born to healthy or COVID-19 infected mothers during the pandemic could also be a contributing factor.

### 6.1.3 Study 3: Prevalence of GORD and the use of anti-reflux medications among preterm infants in neonatal units in England and Wales from 2010-2017

This study aimed to describe the prevalence of GORD diagnosis and use of anti-reflux medications among preterm infants in England and Wales from 2010-2017 by using the National Neonatal Research Database (NNRD). To the best of our knowledge, this is the first and largest attempt at analysing the prevalence of GORD

diagnosis as well as the prescriptions of anti-reflux medications use in England and Wales by using a national database in which 200 units contributed data to the study. I showed that there was a consistent prevalence of GORD diagnosis in the neonatal units from 2010-2017 involving c.4-5% of infants, but there was a higher proportion of infants with recorded anti-reflux medication use at c.10-14% of infants every year. However, there was a fall in the use of anti-reflux medications in general since 2011 which may be related to the emerging evidence on the questionable effectiveness of anti-reflux medications use for preterm infants and increasing studies on adverse effects of the use of most anti-reflux medications including PPI, H2RA and prokinetics.

### 6.1.4 Study 4: A survey on health practitioners' and parents' perspectives on the management of GORD among preterm infants in the neonatal unit

This study which was undertaken as a patient and public involvement activity (PPI) aimed to explore the current practice and perception of health practitioners on the management of GORD among preterm infants, as well as the perception of the parents of preterm infants on the treatment of GORD received during admission in the neonatal unit. The majority of the health practitioners in this study do not use tests to diagnose GORD routinely and mostly base their diagnosis of GORD on clinical features only. To manage GORD, the majority of the health practitioners reported that they first opted for non-pharmacological strategies, before using any anti-reflux medications. The main non-pharmacological strategy chosen was the reduction of the feeding volumes by increasing feed frequency. However, for those who chose pharmacological strategies, the majority chose PPI to manage GORD, followed by feed thickener with antacid such as Gaviscon. As for parents' perspectives, based on the clinical trial scenario given in the study, a higher score was received for an intervention arm ('not giving medications as first approach').

This appears to show that parents have conflicting concerns about the use of medications for GORD for infants or have some background knowledge on the side effects of some anti-reflux medications.

## 6.2 IMPLICATIONS FOR PRACTICE

In study 1, I found that factors that affect the growth outcome at discharge differed between the units in Malaysia and the UK. It is noteworthy to highlight that there was an absence of any measurements of body composition to inform the quality of information of the growth of the infants studied. The optimal pattern of growth needs to balance the overall growth (including head circumference and length growth), while also considering the concerns of cognitive benefits versus the risks of later adverse metabolic programming (403).

The heterogeneous group of preterm infants in this study, differing by gestation, intrauterine growth, and severity of illness, should be noted as the unified approach in the use of standardised nutrition guidelines might not be appropriate as conditions such as CLD, sepsis or the need for ventilation are known to affect the energy requirements. This group of infants might suffer from greater cumulative nutrient deficits, have a longer stay in the unit and poorer growth at discharge. Therefore, more attention to individual nutritional priorities is important.

The lack of use of breast milk fortifier (BMF), even when infants would be eligible to receive BMF under local guidelines, raises the important question that this could be the main cause for the inadequate protein intakes and high cumulative protein deficits showed in this study especially among the UK infants. However, the use of breast milk fortifier itself is controversial, as it might disrupt the normal breastfeeding pattern and current evidence from a systematic review (97) is insufficient to show

whether multinutrient fortification has any effect on long-term growth or neurodevelopment, although short-term increases in weight gain, length gain and head growth were reported.

The practice of aggressive nutrition to push for faster weight gain or catch-up growth and the use of reference growth charts vs standard growth charts (i.e. INTERGROWTH-21) raises an important question if the current practice is appropriate for long term growth whilst avoiding later metabolic consequences.

In Study 2, the effects of visiting restrictions to the neonatal units on the prevalence of breastfeeding during admission and at discharge showed that although there were general reductions in the breastfeeding prevalence among admitted infants during the COVID-19 pandemic, these were not significant. However, it was observed that breastfeeding at any point during admission was not affected by the visiting policy change but breastfeeding at discharge (indicating successful longer-term breastfeeding) had more apparent variation. Therefore, collective efforts in the neonatal unit can be suggested to support breastfeeding mothers, through easier access to the unit for both parents with proper infection control practice (i.e face mask wearing and adequate hand hygiene), clear guidelines on feeding the infant, and milk expression when mothers cannot attend to the unit or when mothers are infected with COVID-19, and more lactation support provided for extended breastfeeding until discharge.

Study 3 demonstrated that the use of anti-reflux medications among preterm infants in neonatal units was higher than the recorded GORD diagnosis. While this included the use of antacid-containing thickeners such as Gaviscon, which some units might regard as a feed thickener instead of medication, this still showed that prescriptions of anti-reflux medications are quite common, despite being unlicensed to use for

neonates. However, with increasing evidence of the associations between the use of anti-reflux medications, specifically H2RA and PPI with negative outcomes, such as infections, necrotising enterocolitis (NEC), and mortality, this pattern of medication use is concerning. Previous studies have shown that infants exposed to these medications experienced higher rates of NEC, infections (including sepsis) and mortality (201,203,208), but some results were contradictory (205,209). These studies were, however, limited by their designs such as case-control studies that had different criteria for selection of comparison groups that might lead to bias, as well as retrospective studies that had limited data to account for many confounding factors.

Study 3 also showed that some infants who had recorded anti-reflux medications did not have GORD diagnosis recorded but most infants with a recorded GORD diagnosis received the prescriptions of anti-reflux medications. Therefore, this highlights an important question surrounding GORD diagnosis in neonatal units and whether it was made based on non-specific clinical features or symptoms of the infants alone, following tests/investigations such as pH measurement, or using a trial of treatment. Clear guidelines in determining, or confirming, the diagnosis of GORD is important to ensure that medications will not be overprescribed, non-specific clinical features inappropriately treated or physiological reflux not overtreated. The role of clinicians in providing enough assurance and adequate information to the parents on the stepwise management while avoiding unnecessary pharmacological treatments is highly recommended.

In Study 4, the self-reported survey showed that health practitioners, in general, preferred the use of a non-pharmacological approach as a first step in managing GORD and parents of preterm infants also showed preference to the use of non-pharmacological therapy as the initial approach in managing GORD instead of anti-

reflux medications. Although this is not in accordance with the results of Study 3 which identified high use of anti-reflux medications, this might indicate that there is awareness of the importance of using a stepwise approach in managing GORD in preterm infants as per practice guidelines.

In addition, considering that parents reported some understanding of the use of non-pharmacological strategies in treatment for GORD and expressed concerns on possible side-effects of some anti-reflux medications, clear information and reassurance from health practitioners is needed in parental communications when managing GORD in preterm infants.

## 6.3 IMPLICATIONS FOR FUTURE RESEARCH

From the four studies included in this thesis, several suggestions for future research are proposed as below.

There is an urgent need to conduct adequately powered large-scale collaborative trials on the effects of nutritional interventions, using short term markers that can be reflective of longer-term outcomes. In general, some of the outstanding areas of research include the routine use of breast milk fortifier (BMF) on long term growth/neurodevelopment, effects of the use of BMF originated from human breast milk vs cow's milk-based on the incidence of NEC, and the routine use of donor breast milk vs PN in the early postnatal days while waiting for mother's own milk (MOM). The use of the recently proposed standard growth chart for preterm infants (INTERGROWTH-21) in the large multi-countries study is also important to observe if the effect of nutritional interventions on growth differ and the rate of postnatal growth failure is better than when using reference charts.

Following the findings from the Malaysian unit, more research is needed to study the effects of aggressive nutrition on short term growth and longer-term growth and neurodevelopment as well as post-discharge nutrition among preterm infants. For the UK unit, a comparison study on the normal use of BMF vs proactive use of the BMF as per the local guideline would show if protein intakes can be improved and cumulative protein deficits can be minimised, especially among seemingly healthy preterm infants. Forthcoming collaborative UK-Malaysia study on the 6-months and 2-years follow-up growth after discharge of the same cohorts of infants in both units are in planning.

From Study 2, further studies on the effects of COVID-19 on the prevalence of breastfeeding in the neonatal unit should be continued by including more units with a larger number of admitted infants to increase sample size and a longer period of observation. In addition, a comparison of units that implement different or more restrictive visiting policies and clear hindrance to direct breastfeeding especially among infants born to COVID-19 infected mothers would be valuable to observe, if there are any apparent effects towards the prevalence of breastfeeding and extended breastfeeding at discharge and up to 3-6 months post-discharge. Characteristics of mothers and infants could also be different, and this may help in facilitating better analysis.

From Study 3, considering the high prevalence of use of anti-reflux medications shown in the NNRD cohort from 2010-2017, there is a necessity to explore the possible association between their routine prescription with adverse effects on infants in UK neonatal units such as the occurrence of necrotising enterocolitis (NEC) and infections. An application for data from the NNRD to conduct this study has been initiated and ethical approval has been received by this student. This study is expected to commence in October 2021. Ethical approval is received from

Yorkshire & The Humber – South Yorkshire Research Ethics Committee 21/YH/0055 (Appendix 10).

In addition, from my observation that the rate of use of anti-reflux medications has been declining since 2011, potentially due to the increasing evidence of adverse effects published in studies as well as national and local guidelines which emphasised the contradictions of its use, a future study could investigate the variation between units in the management of GORD, specifically in the use of anti-reflux medications and the consistency in practice based on standard protocol/guideline use on the management of GORD.

On the other hand, after the general decline in medication use, the rate was seen to be stable from 2016 to 2017, therefore further investigation towards medication use after this year should be continued to see if effects on the practices in the neonatal unit following recommendations and studies on adverse effects might exert restorative effect after the declined use. In addition, future work to look at the impact of the recall of H2RA (ranitidine), as well as an indirect effect of this recall on the use of other types of medication/thickener, should also be studied.

From the PPI survey study (Study 4), a proposed clinical trial in determining the effectiveness of non-pharmacological strategy vs pharmacological strategies in managing GORD in preterm infants can be performed, considering well-communicated information on the outcome preferred as showed in the survey which is “reduced reflux symptoms”. Additionally, despite a high percentage of parents who agreed to be involved in the proposed trial, an alternative to the computer-generated therapy chosen for the infants should be considered as it showed unfavourable feedbacks from the parents for this approach for the blinded treatment.

Overall, from these PhD studies, other than my prospective observational and survey studies, I have been able to venture into new epidemiological fields of study in which analyses of both small and large databases were performed using the National Neonatal Research Database (NNRD) and BadgerNet. NNRD has been validated and widely used for many retrospective studies. However, improvements are needed in the aspect of detailed information for daily care variables such as nutritional intakes for both enteral feeding and parenteral i.e on a volume of PN, IV glucose and milk received, breast milk fortifier use, frequency and dosages of medication use, as well as complete information for longer-term follow-up growth and feeding information. It will also be valuable if linkage to other data sources such as general practitioner (GP) data – The General Practice Research Database (GPRD) or data from this program: https://digital.nhs.uk/services/national-child-measurement-programme/ is made available. This would make feasible post-discharge studies and studies that need larger sample sizes and continuation of observations at the community level without the need for costly and time-consuming follow-up of small cohorts.

In my home country, Malaysia, there is also a national neonatal registry known as the Malaysian National Neonatal Registry (MNNR) which was established in 2003 under the Ministry of Health. However, as the main aim is to provide an archive of population-based disease registry for the neonatal population, the data of infants who were admitted to the neonatal units included in this database were based on any of these criteria (inborn or outborn infants): gestational age (<32 weeks GA only), birth weight (500-1500g), those requiring respiratory support, infants with hypoxic ischaemic encephalopathy (HIE), infants with confirmed sepsis, those with congenital heart disease, and all neonatal deaths.  Therefore, the data provided in

the database are not inclusive for all preterm infants or infants admitted to neonatal units.

The data collection is also performed by using Case Report Forms (paper-based) that need to be returned to the main MNNR office every month which makes the process of data collection challenging, as opposed to the electronic system operated from NHS to NNRD (UK). Therefore, while this may take some time, improvements are needed to improve this database considering that many hospitals have been switching to the electronic system such as the Total Hospital Information System (THIS) called Caring Hospital Enterprise System (C-HEtS) that I used in the first study (Chapter 2).

Nevertheless, although improvements are needed for a more efficient system, data collected from this registry so far has been utilised in many research studies for the neonatal population in Malaysia, but limited studies were undertaken on neonatal nutrition and growth. Therefore, I would anticipate that after the completion of my studies, I could initiate the study on this area using MNNR, utilising the skills that I have learned from my previous PhD project in using NNRD for a larger national study.

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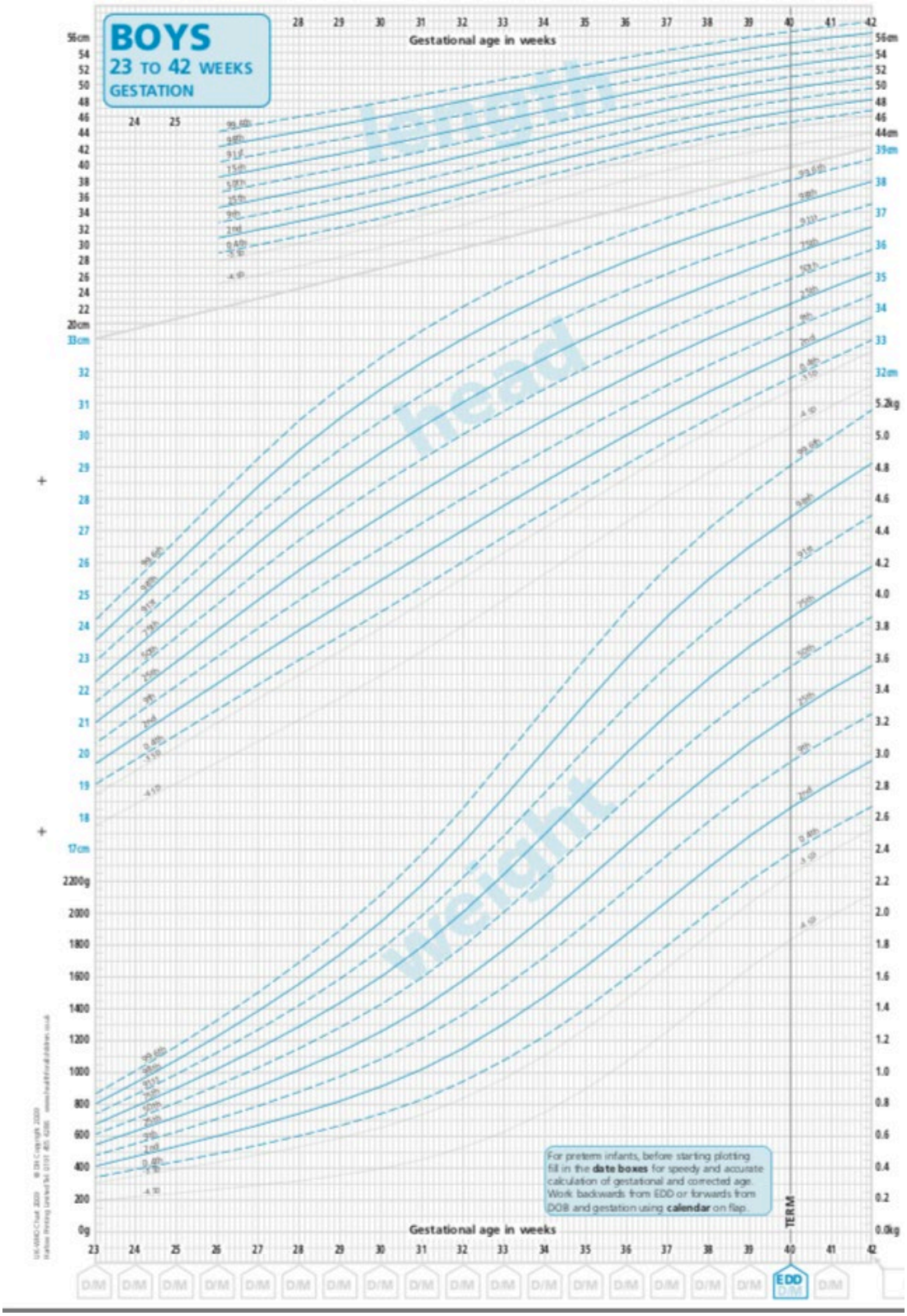
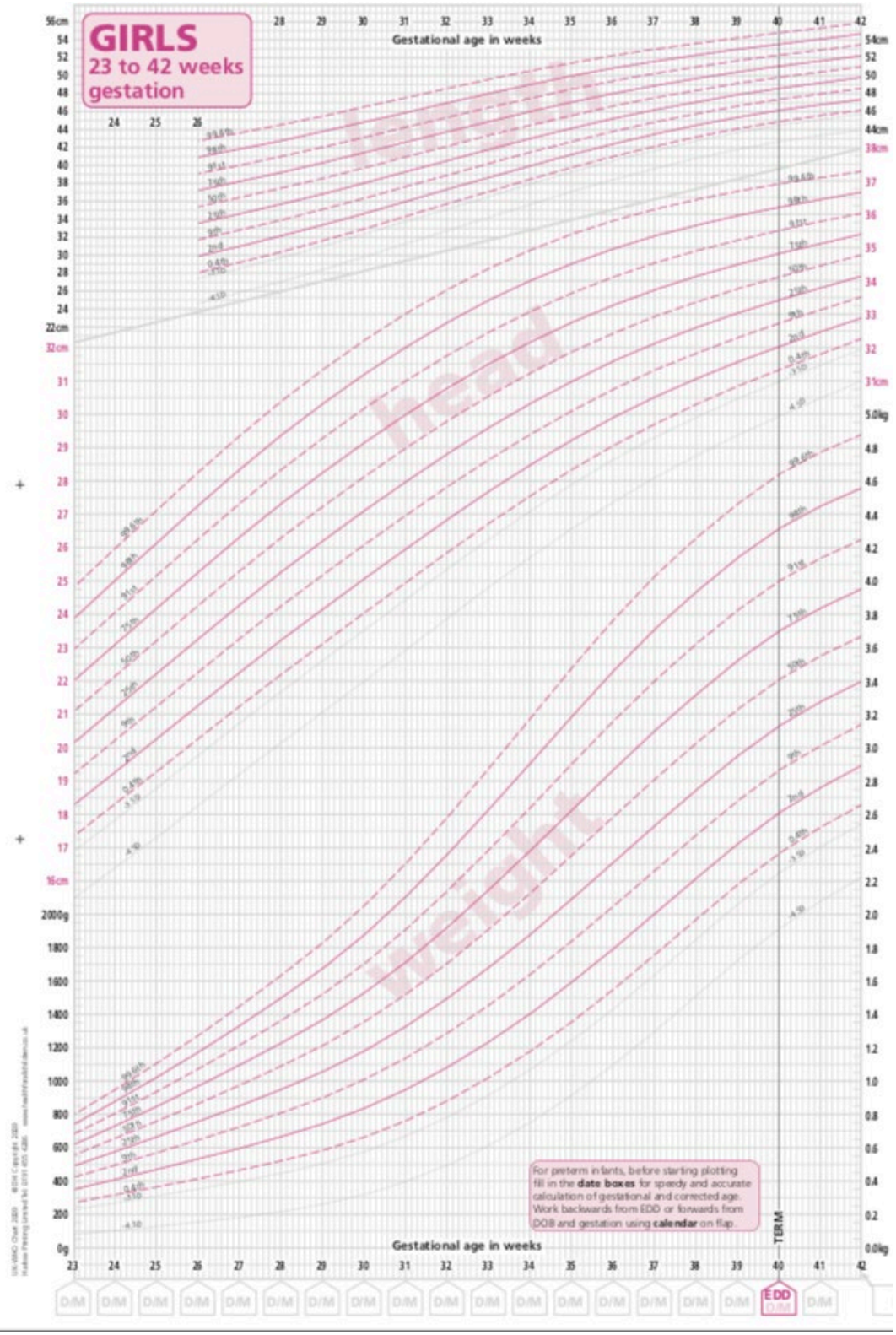
## APPENDICES

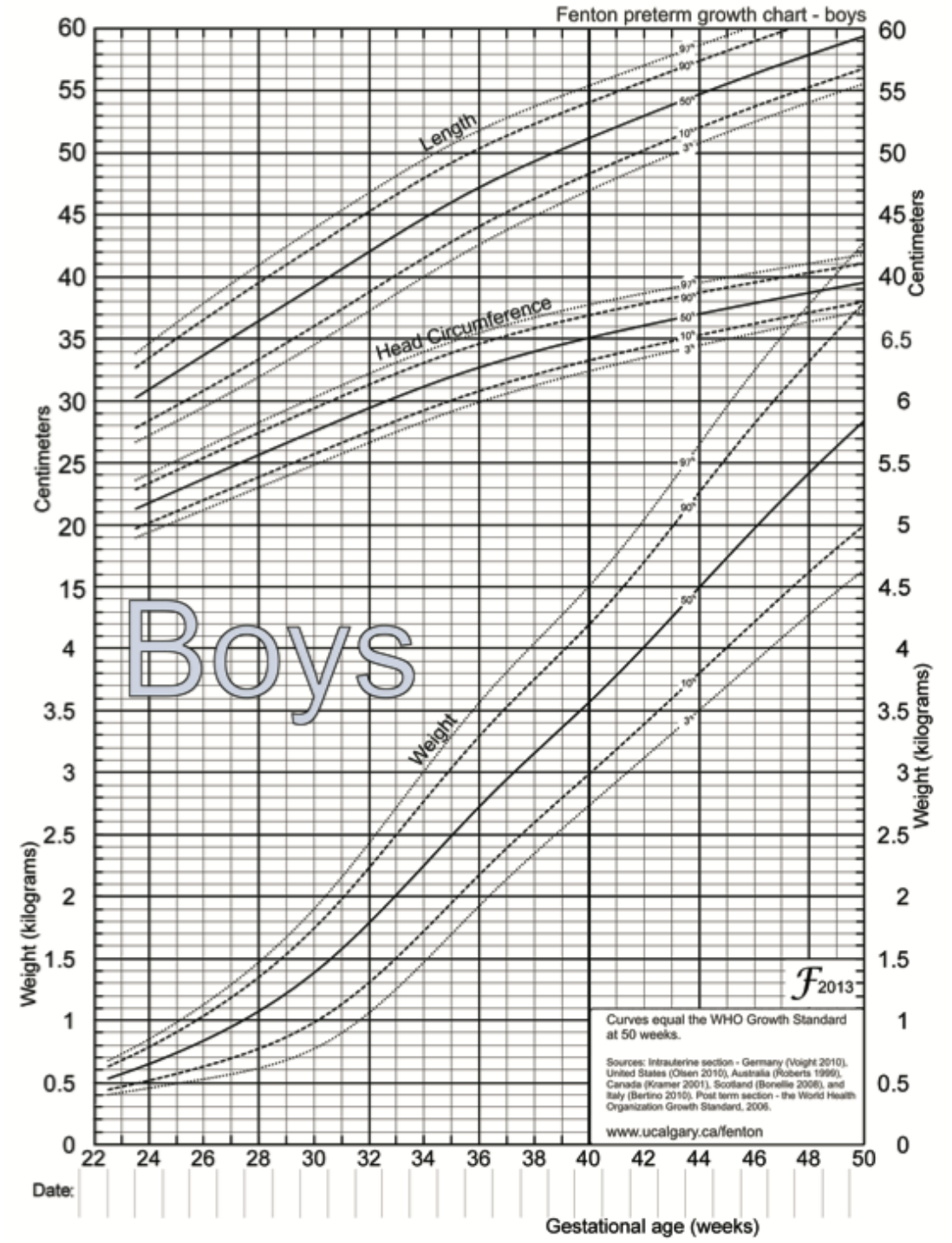
### Appendix 1 : Growth charts for preterm infants

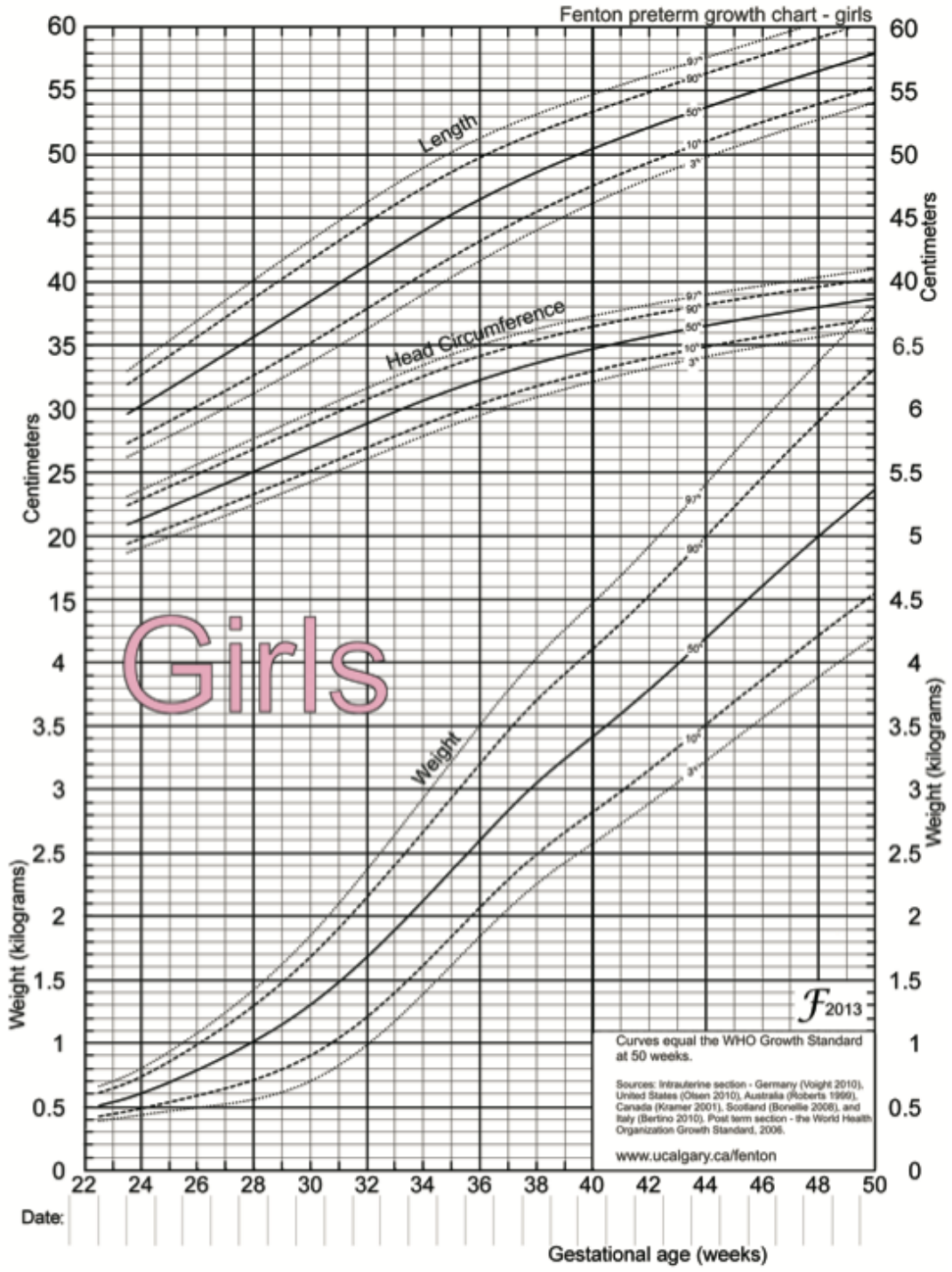
Neonatal and Infant Close Monitoring Growth Chart (UK-WHO)



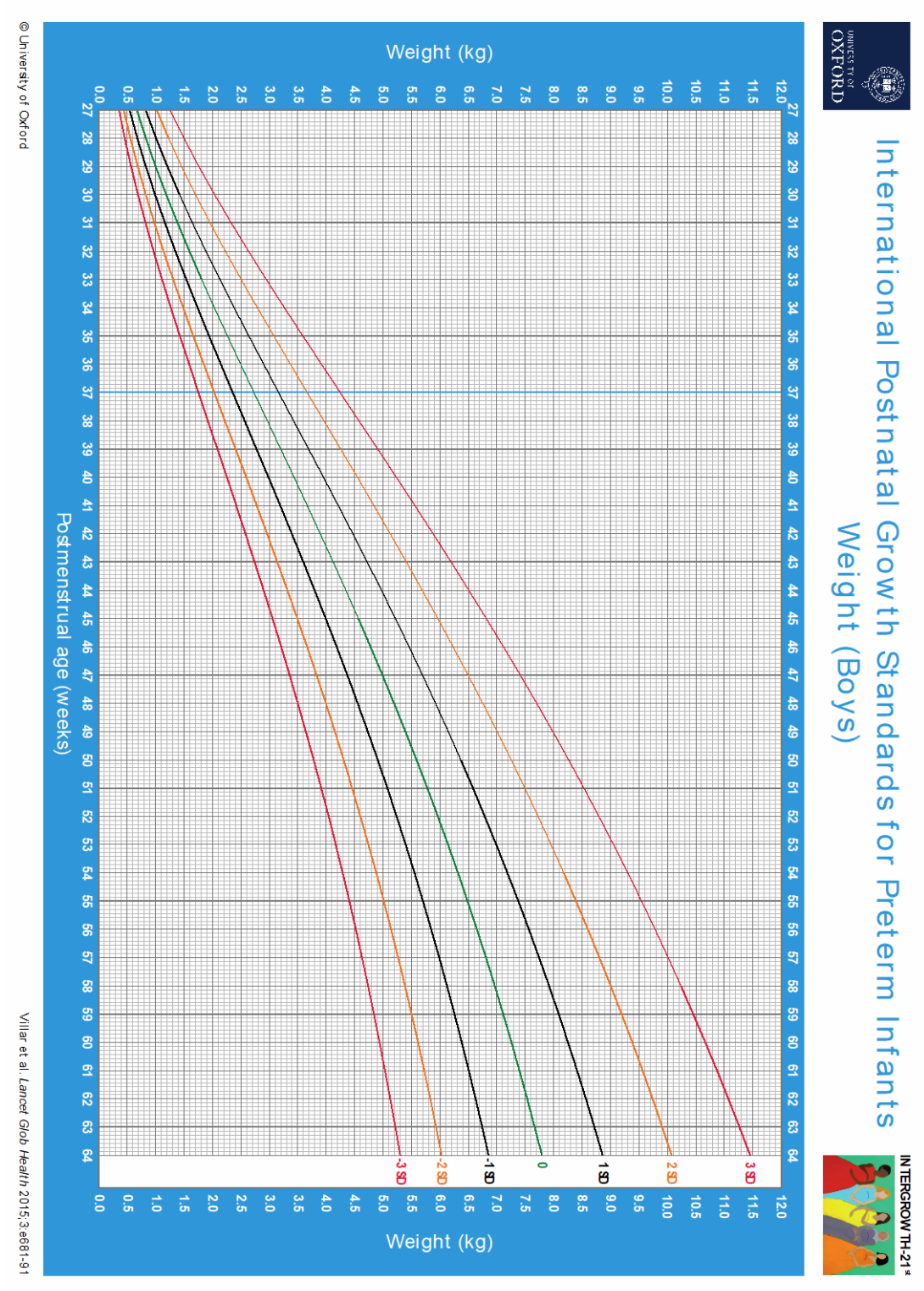

GIRLS
23 to 42 weeks gestation
Gestational age in weeks
head
weight
For preterm infants, before starting plotting fill in the date boxes for speedy and accurate calculation of gestational and corrected age. Work backwards from EDD or forwards from DOB and gestation using calendar on flap.
TERM
EDD

Fenton Growth Chart



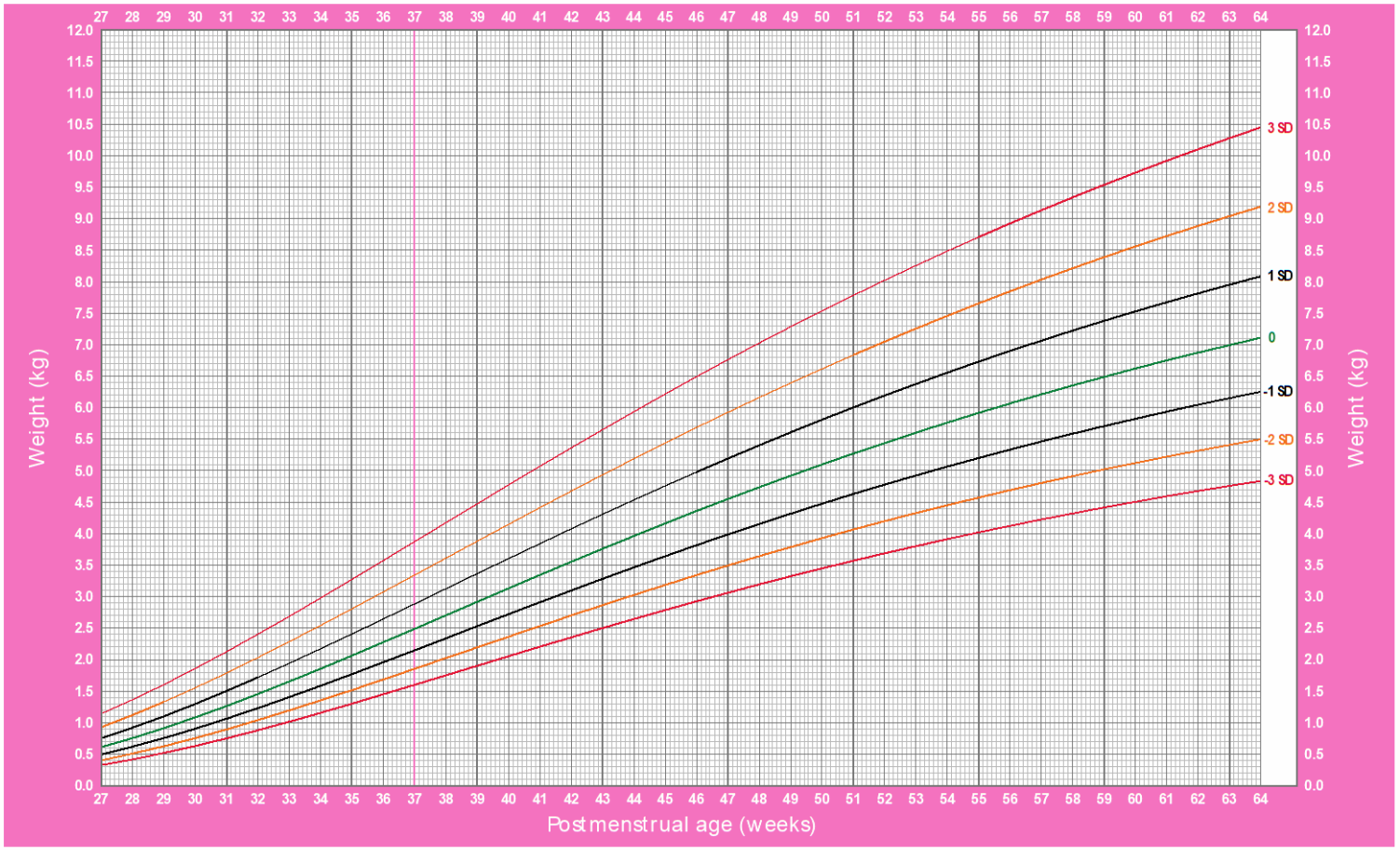

Fenton preterm growth chart - girls
Length
Head Circumference
Weight
Girls
Centimeters
Weight (kilograms)
Date:
Gestational age (weeks)
Curves equal the WHO Growth Standard at 50 weeks.
Sources: Intrauterine section - Germany (Voigt 2010), United States (Olsen 2010), Australia (Roberts 1999), Canada (Kramer 2001), Scotland (Bonellie 2008), and Italy (Bertino 2010). Post term section - the World Health Organization Growth Standard, 2006.
www.ucalgary.ca/fenton
2013

INTERGROWTH Preterm Growth chart



# International Postnatal Growth Standards for Preterm Infants
## Weight (Girls)

INTERGROWTH-21st






Villar et al. *Lancet Glob Health* 2015;3:e681-91

## Appendix 2: HRA approval letter for Nutrition and growth study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Shalini Ojha
Division of Graduate Entry Medicine
Derby Medical School
Derby
DE22 3DT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

21 February 2019

Dear Dr Ojha

**HRA and Health and Care Research Wales (HCRW) Approval Letter**

| | |
|---|---|
| **Study title:** | **Nutrition and Growth in preterm infants: an observational study of nutritional practices and growth in preterm infants admitted to NICU** |
| **IRAS project ID:** | **258817** |
| **Protocol number:** | **19012** |
| **Sponsor** | **University of Nottingham** |

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

**How should I continue to work with participating NHS organisations in England and Wales?**
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

**Appendix 3: Agreement letter for UK-Malaysia Nutrition and growth study**

UNIVERSITI KEBANGSAAN MALAYSIA
*The National University of Malaysia*

**SULIT**

PEJABAT PRO NAIB CANSELOR (KAMPUS KUALA LUMPUR) • *PRO VICE CHANCELLOR OFFICE (KUALA LUMPUR CAMPUS)*

**UKM.KKL.100-1/13/4/FP963**
12 November 2019

Mr. Ben Sumner
Research & Innovation
Director Corporate Partnerships
Research & Innovation Group-Jubilee Campus
East Atrium, Jubilee Conference Centre
Triumph Road, Nottingham
NG8 1DH, United Kingdom

Dear Sir,

**Project Agreement Between UKM and University of Nottingham**
**Co. Researcher : Prof. Dr. Cheah Fook Choe**
**Student : -**
**Project Title : Nutrition and Growth in Preterm Infants: An Observational Study of Nutritional Practices and Growth in Preterm Infants Admitted to NICU in the UK and Malaysia**
**Project Code : FF-2019-247**

We refer to the above matter.

Herewith enclosed an original copy of the Project Agreement between UKM and University of Nottingham for your safe keeping.

Thank you.

Yours Faithfully,

**NURHUSNA BINTI ZAINAL ABIDIN**
Executive (Legal)
Legal Office
Kuala Lumpur Campus

- *Attachment*

*s/k* -
YBhg. Prof. Dr. Cheah Fook Choe
Paediatrics Department
Hospital Canselor Tuanku Muhriz

**SULIT**

**PEJABAT UNDANG-UNDANG, KAMPUS KUALA LUMPUR**
Tingkat 1, Kompleks Pendidikan Perubatan Canselor Tuanku Ja'afar, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras Kuala Lumpur, Malaysia
Telefon: +603-9145 5010/5011/5131/5139/6966 Faksimili: +603-9145 5757 E-mel: hafiza@ppukm.ukm.edu.my, husna.z.abidin@ppukm.ukm.edu.my, ummufarahfais@ukm.edu.my, puu@ppukm.ukm.edu.my, kpuu@ppukm.ukm.edu.my Laman Web: http://www. ukm.my/provckl

## Appendix 4: Feeding protocol ( HCTM neonatal unit)

| Bolus group | per day | Continuous group (3+1 cycle) | per day |
|---|---|---|---|
| 1 ml 6 hourly* | 4 ml | Same as bolus group | 4 ml |
| 1 ml 4 hourly* | 6 ml | Same as bolus group | 6 ml |
| 1ml 3 hourly* | 8 ml | Same as bolus group | 8 ml |
| 1ml 2 hourly | 12 ml | Same as bolus group | 12 ml |
| | | **INFUSION FEEDING 3 hours, REST 1 hour** | |
| 2ml 2 hourly | 24 ml | 1.3ml/hr | 23.4 ml |
| 3ml 2 hourly | 36 ml | 2.0ml/hr | 36.0 ml |
| 4 ml 2 hourly | 48 ml | 2.7ml/hr | 48.6 ml |
| 5 ml 2 hourly | 60 ml | 3.3ml/hr | 59.4 ml |
| 6 ml 2 hourly | 72 ml | 4.0ml/hr | 72.0 ml |
| 7 ml 2 hourly | 84 ml | 4.7ml/hr | 84.6 ml |
| 8 ml 2 hourly | 96 ml | 5.3ml/hr | 95.4 ml |
| 9 ml 2 hourly | 108 ml | 6.0ml/hr | 108.0 ml |
| 10 ml 2hourly | 120 ml | 6.7ml/hr | 120.6 ml |
| 11 ml 2 hourly | 132 ml | 7.3ml/hr | 131.4 ml |
| 12 ml 2 hourly | 144 ml | 8.0ml/hr | 144.0 ml |
| 13 ml 2 hourly | 156 ml | 8.7ml/hr | 156.6 ml |
| 14 ml 2 hourly | 168 ml | 9.3ml/hr | 167.4 ml |
| 15 ml 2 hourly | 180 ml | 10.0ml/hr | 180.0 ml |
| 16 ml 2 hourly | 192 ml | 10.7ml/hr | 192.6 ml |
| 17 ml 2 hourly | 204 ml | 11.3ml/hr | 203.4 ml |
| 18 ml 2 hourly | 216 ml | 12.0ml/hr | 216.0 ml |
| 19 ml 2 hourly | 228 ml | 12.7ml/hr | 228.6 ml |
| 20 ml 2 hourly | 240 ml | 13.3ml/hr | 239.4ml |
| 21 ml 2 hourly | 252 ml | 14.0ml/hr | 252.0 ml |
| 22 ml 2 hourly | 264 ml | 14.7ml/hr | 264.6 ml |
| 23 ml 2 hourly | 276 ml | 15.3ml/hr | 275.4 ml |
| 24 ml 2 hourly | 288 ml | 16.0ml/hr | 288.0 ml |
| 25 ml 2 hourly | 300 ml | 16.7ml/hr | 300.6 ml |
| | | | |

**Trophic feeds were given as bolus in both arms until a feed volume of 12ml/day was reached after which the infant followed the regime assigned*

**Infusion feeding USING EBM**

For patients on infusion feeding **using EBM**

- Preparation of milk for the day to be pasteurized → **TOTAL VOLUME + extra 15 ml**
- For PK to divide milk into **SIX (6) bottles**
- Feeding time (Infusion 3 hours, REST 1 hour) :
    - Infusion feeding 0600-0900H, rest 0900-1000H
    - Infusion feeding 1000-1300H, rest 1300-1400H
    - Infusion feeding 1400-1700H, rest 1700-1800H
    - Infusion feeding 1800-2100H, rest 2100-2200H
    - Infusion feeding 2200-0100H, rest 0100-0200H
    - Infusion feeding 0200-0500H, rest 0500-0600H

- The staff nurse that STARTS the infusion feeding is to syringe the EBM out from the bottle to 3 different syringes. Warm the FIRST syringe and keep the other two syringes capped in the fridge. When needing to change syringe after one hour then warm the 2nd syringe for change.

- ONE perfusor tubing may be used for ONE whole cycle (3+1hr rest)

**Infusion feeding USING P22/P24k**

For patients on infusion feeding **using P22/P24k** (once opened, may be used up to 4 hours)

- Syringe total volume for 3 hours and infuse over 3 hours using rate prescribed by the doctor
- USE THE SAME SYRINGE for 3 hours
- ONE perfusor tubing may be used for ONE whole cycle (3+1hr rest)

Handling of infusion feeding

1. Sterile technique
    - Wash/Sanitize hands
    - Use NON-TOUCH technique between syringe tip and tubing end
    - Not necessary to wear sterile gloves

**Guidelines extracted from Paediatric Protocols for Malaysian Hospitals (4th Edition, 2018).**

**When to start milk?**

• As soon as possible for the well term babies

• However, in very preterm infants there may be an increased risk for NEC if feeding is advanced too rapidly, although early feeds with EBM is to be encouraged. Studies suggest that rapid increments in feeds has a higher risk for NEC than the time at which feeding was started.

• Start trophic feeding preferably within 24 hours if EBM available. Caution in ELBW babies or growth- restricted infants. If by 24-48 hours, and no EBM is available, consider a premature formula milk

• Minimal enteral feeding (MEF) is recommended in very preterm infants. The principle is to commence very low volume enteral feeds on day 1 - 3 of life (i.e. 5 - 25 ml/kg/day) for both EBM and formula milk. MEF enhances gut DNA synthesis hence promotes gastrointestinal growth. This approach allows earlier establishment of full enteral feeds and shorter hospital stays, without any concomitant increase in NEC.

**How much to increase?**

• Generally, the rate of increment is about 20 to 30 mls/kg/day.

• Well term babies should be given breastfeeding on demand.

• Milk requirements for babies on full enteral feed from birth:

Day 1: 60 ml/kg/day

Day 2 - 3: 90 ml/kg/day

Day 4 – 6: 120 ml/kg/day

Day 7 onwards: 150 ml/kg/day

Add 15% if the baby is under phototherapy

• In babies requiring IV fluids at birth: The rate of increment need to be individualized to that baby.

• Babies should be observed for feeding intolerance (vomit or large aspirate) and observe for any abdominal distention before increasing the feed.

**What is the maximum volume?**

• Target weight gain should be around 15g/kg/day (range 10-25g/kg/day). Less weight gain than this suggests a need to increase calories especially protein calories. More weight gain than 30g/kg/day should raise the possibility of fluid overload particularly in babies with chronic lung disease.

• Preterm infants: Increase feed accordingly to 180 to 200 mls/kg/day. (This should only be achieved by Day 10 to Day 14 respectively if baby had tolerated feeds well from Day 1). If on EBM, when volume reaches 75 mls/kg/day: add HMF.

**Human Milk Fortifier (HMF)**

• It is recommended to add HMF to EBM in babies < 32 weeks or < 1500 grams.
• HMF will give extra calories, vitamins, calcium and phosphate.
• HMF should be added to EBM when the baby is feeding at 100 ml/kg/day.
• Start HMF at concentration of 1 sachet: 50 ml EBM and if this is tolerated for 48 hours, increase to 1:25. Check the dilution as it may vary between different brands.
• VLBW infants on exclusive breastmilk may require sodium supplementation until 32-34 weeks corrected age.

**Infant Formula**

• Infant formula should only be given if there is no supply of EBM. There are 2 types of infant formula: Preterm formula and Normal Term Formula.
• Preterm formula: for babies born < 32 weeks or < 1500 grams.
• Normal infant formula: for babies born ≥ 32 weeks or > 1500 grams.

**When to stop HMF or Preterm Formula?**

• Consider changing preterm to standard formula and stop adding HMF to EBM when babies are breastfeeding on demand or have reached their expected growth curve.

• Preterm with poor weight gain can be given specially formulated post discharge formula for preterm infants. Preterm formula meant for newborn preterm infants should not be given to infants > 2 months post conceptual age in view of potential Vitamin A and D toxicity.

**Vitamin and mineral supplementation**

• Vitamins: a premature infant's daily breast milk/ breast milk substitute intake will not supply the daily vitamin requirement. Multivitamin drop providing Vitamin D 400 IU per day can be given after day 14 of life when on feeding of 150 mls/kg/day. The supplement is continued for 3-4 months post discharge.

• Iron: Babies of birth weight < 2000g should receive iron supplements. Iron is given at a dose of 3 mg/kg elemental iron per day. Ferric Ammonium Citrate (400mg/5mls) contains 86 mg/5 mls of elemental iron. Start on day 28, continue until 3-4 months post discharge or until review. Babies who have received multiple blood transfusions may not require as much iron supplementation.

Special Cases

• IUGR babies with reversed end-diastolic flow on antenatal Doppler: Studies have showed that these babies are at risk of NEC. Thus, feeds should be introduced slowly and initially use only EBM.

**Indication for TPN**

• Birth weight < 1000 gm
• Birth weight 1000-1500 gm and anticipated to be not on significant feeds for 3 or more days.
• Birth weight > 1500 gm and anticipated to be not on significant feeds for 5 or more days.
•Surgical conditions in neonates: necrotizing enterocolitis, gastroschisis, omphalocoele, tracheo-esophageal fistula, intestinal atresia, malrotation, short bowel syndrome, meconium ileus and diaphragmatic hernia.

**Prescription**

TPN can be delivered using standardised or individualised bags.

**Goal**: to provide 120-130 Kcal/kg/day, to start TPN within the first 24 hours of life in the smaller preterm infants <1250 grams birth weight.

• 10% Dextrose solution provides 0.34 Kcal/ml.

• 10% Lipid solution gives 0.9 Kcal/ml;

• 20% lipid solution gives 1.1 Kcal/ml.

• Protein/Energy ratio: 3-4 g/100 Kcal is needed to promote protein accretion. A baby given only glucose will lose 1.5 grams body protein/day.

**Fluid**

• Usually started at 60-80 ml/kg/day (if newborn), or at whatever stable fluid intake the baby is already receiving.

• Postnatal weight loss of 5 - 15 % per day in the ELBW is acceptable.

• Volumes are increased over the first 7 days in line with the fluids and electrolytes protocol with the aim to deliver 120-150 ml/kg/day by day 7.

**Amino acids**

• Protein is usually started at 2g/kg/day of crystalline amino acids and subsequently advanced, by 3rd to 4th postnatal day, to 3.0 g/kg/day of protein in term and by 5th day 3.7 to 4.0 g/kg/day in the extremely low birthweight (ELBW) infants.

**Glucose**

• In the ELBW minimum supply rate is 6 mg/kg/min to maintain adequate energy for cerebral function; additional 2-3 mg/kg/min (25 cal/kg) of glucose per gram of protein intake is needed to support protein deposition.

• Maximum rate: 12 - 13 mg/kg/min (lower if lipid also administered) but in practice often limited by hyperglycaemia.

• Glucose administration is started at 6 mg/kg/min, advancing to 12-14 mg/kg/min and adjusted to maintain euglycaemia.

• If hyperglycaemia develops glucose infusion is decreased. Insulin infusion is generally not required if sufficient proteins are given and less glucose is administered during the often transient hyperglycaemia. Insulin infusion, if used for persistent hyperglycaemia with glycosuria, should be titrated to reduce risk of hypoglycaemia.

**Lipid**

• Start lipids at 1g/kg/day, at the same time as amino acids are started, to prevent essential fatty acid deficiency; gradually increase dose up to 3 g/kg/day (3.5g/kg/day

in ELBW infants). Use smaller doses in sepsis, compromised pulmonary function, hyperbilirubinaemia.

• It is infused continuously over as much of the 24-hour period as practical.

• Avoid concentrations >2g/kg/day if infant has jaundice requiring phototherapy.

• Preparation of 20% emulsion is better than 10% as 20% solutions require less fluid volume and provide a lower phospholipid-to-triglyceride ratio. 10% solution interferes with triglyceride (TG) clearance leading to higher TG and cholesterol values. Use of preparations containing lipids from fish oil and olive oil may reduce the risk of cholestasis with prolonged TPN.

• Heparin at 0.5 to 1 units/mL of TPN solutions can facilitate lipoprotein lipase activity to stabilize serum triglyceride values. The final concentration of heparin used may need to decrease to 0.5 units/ml in small neonates receiving larger TPN volumes in order to avoid approaching therapeutic amount.

• Lipid clearance monitored by plasma triglyceride (TG) levels. (Max TG concentration ranges from 150 mg/dl to 200 mg/dl).

**Electrolytes**

• The usual sodium need of the newborn infant is 2-3 mEq /kg/day in term and 3-5 mEq/kg/day in preterm infants after the initial diuretic phase (first 3-5 days). Sodium supplementation should be started after initial diuresis (usually after the 48 hours), when serum sodium starts to drop or at least at 5-6% weight loss. Failure to provide sufficient sodium may be associated with poor weight gain.

• Potassium needs are 2-3 mEq/kg/day in both term and preterm infants. Start when urine output improves after the first 2-3 days of life.

**Minerals, Calcium (Ca), Phosphorus (P) And Magnesium**

• In extrauterine conditions, intrauterine calcium accretion rates are difficult to attain. Considering long-term appropriate mineralization and the fact that calcium retention between 60 to 90 mg/kg/day suppresses the risk of fracture and clinical symptoms of osteopenia, a mineral intake between 65 to 75 (elemental) mg/kg/day of highly-absorbed calcium and 60 to 75 mg/kg/day of phosphorus could be recommended.

• The optimal ratio of Calcium to Phophorus is generally between 1:1.3 and 1:1.7 by weight and nearly a 1:1 molar ratio.

• Monitoring for osteopaenia of prematurity is important especially if prolonged PN.

• A normal magnesium level is a prerequisite for a normal calcaemia. In well balanced formulations, however, magnesium level does not give rise to major problems.

**Trace Elements**

• Indicated if PN is administered for ≥ 1 week. Commercial preparations are available.

**Vitamins**

• Both fat- and water-soluble vitamins are essential. It should be added to the fat infusion instead of amino-acid glucose mixture to reduce loss during administration.

**Administration**

• TPN should be delivered where possible through central lines.

• Peripheral lines are only suitable for TPN ≤ 3 days duration and dextrose concentration ≤ 12.5%.

• Peripheral lines are also limited by osmolality (<600 mOsm/L) to prevent phlebitis.

• Percutaneous central line: confirm catheter tip position on X-ray prior to use.

• Ensure strict aseptic technique in preparation and administration of TPN.

• Avoid breakage of the central line through which the TPN is infused, though compatible drugs may be administered if necessary.

UNIVERSITI KEBANGSAAN MALAYSIA MEDICAL CENTRE
PHARMACY DEPARTMENT ASEPTIC SERVICES (03-9145 6702/6701)

# TPN ORDER FORM FOR PRE-TERM NEONATES
# (34 WEEKS AND BELOW GESTATIONAL AGE)

| NAME : | R/N : | |
|---|---|---|
| WEIGHT : | DATE OF BIRTH : | AGE (at the time of current TPN order): |
| Gestational Age at birth: ____ weeks | | |

| WARD : | BED NO : |
|---|---|

SEX : ☐ M ☐ F

Route : ☐ Central/PICC/UVC ☐ Peripheral IV

DIAGNOSIS : _____

FIGURES ARE PER *KG* PER 24 HOURS

| DATE : | | | | | | NOTES : |
|---|---|---|---|---|---|---|
| REGIMEN ORDERED | | | | | | |
| Fluid for TPN (ml) | | | | | | |
| DOCTOR'S NAME | | | | | | |
| SIGNATURE | | | | | | |
| Comments: | | | | | | |

| STANDARD REGIMEN / 24hrs [1] | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Protein (*g/kg*) | 2.0 | 2.5 | 3.0 | 3.5 | 3.5 |
| Carbohydrate (%) | 10% | 10% | 12.5% | 12.5% | 12.5% |
| Peditrace (*ml/kg*) | 1 | 1 | 1 | 1 | 1 |
| Sodium **Acetate** (*mmol/kg*) [2] | 1 | 1 | 2 | 2 | 3 |
| Potassium (*mmol/kg*) * | **1.0** | **1.0** | **2.0** | 2.0 | 3.0 |
| Calcium (*mmol/kg*) | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| Magnesium (*mmol/kg*) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Phosphate (*mmol/kg*) | 0.4 | 0.4 | 0.6 | 0.6 | 1.0 |
| Solivite (*ml/kg*) | 1 | 1 | 1 | 1 | 1 |
| Vitalipid N Infant (*ml/kg*) | 1 | 1 | 1 | 1 | 1 |
| Lipid (*g/kg*) | 1.0 | 2.0 | 3.0 | 4.0 | 4.0 |

* For all ELBW (<1kg) infants, and preterm infants with renal impairment, **OMIT potassium for Days 1-3**, unless special requests.
[1]: Regimen 1 for day 1 on TPN, regimen 2 for day 2 and so forth, regimen 5 for day 5 onwards.
[2]: **Sodium Acetate** is used by default. Contact the Pharmacy to switch to Sodium Chloride.
*Additional notes:*
- Dextrose (10 - 12.5 %) recommended for peripheral line
- Regimens will be supplied as 2-in-1 bags with separate lipid syringes, to be infused together

| DATE :<br>ALTERATION in REGIMEN | | | | | |
|---|---|---|---|---|---|
| Protein (*g/kg*) | | | | | |
| Carbohydrate (%) | | | | | |
| Peditrace (*ml/kg*) | | | | | |
| Sodium (*mmol/kg*) | | | | | |
| Potassium (*mmol/kg*) | | | | | |
| Calcium (*mmol/kg*) | | | | | |
| Magnesium (*mmol/kg*) | | | | | |
| Phosphate (*mmol/kg*) | | | | | |
| Solivito (*ml/kg*) | | | | | |
| Vitalipid N Infant (*ml/kg*) | | | | | |
| Lipid (*g/kg*) | | | | | |

*REF: ESPGHAN GUIDELINES on Paediatric Parenteral Nutrition (2018), Comparison between Sodium Acetate and Sodium Chloride in Parenteral Nutrition for Very Pre-Term infants on the Acid-Base Status and Neonatal Outcomes, Adli, EY Ong, Birinder Kaur and Cheah FC (2020)*
Last edited: 15.10.2020

**Appendix 5: Feeding protocol ( RDH neonatal unit)**

**Guidelines extracted from: Enteral Feeding of Preterm & Growth Restricted Infants - Paediatric Full Clinical Neonatal Guideline**

**Starting and advancing enteral feeds**

- Infants >34 weeks gestation

- These infants can usually start nutritive feeds immediately after birth
- Trophic/minimal enteral feeding is not required.
- Slower establishment of enteral feeding may be considered in specific clinical situations, such as critically ill infants e.g. high inotrope requirement, suspected or proven NEC e.g. significant abdominal distension treated as NEC or intestinal obstruction

- Infants < 34 weeks gestation

- Trophic/minimal enteral feeding is defined as volumes of milk feeds (10-15 ml/kg/d) and should be started within first 24 hours of life. Early enteral feeding at such volumes does not aim to meet the nutritional needs of the infant and should be given in conjunction with parenteral nutrition.
- In infants <34 weeks who are IUGR (<2$^{nd}$ centile) and/or have A/REDF, trophic/minimal enteral feeds should be started as soon as possible if mother's expressed breast milk is available. Delay for 24 hours if mother's milk is not available or while awaiting mother's milk may be acceptable.

**Contraindications of trophic feeds**

• Intestinal obstruction
- Respiratory distress, sepsis, hypoglycaemia, umbilical lines are **NOT** contraindications for trophic feeds.

**Recommendation:**

- All preterm infants should be given trophic feeds with mother's own breast milk within 24 hours of birth.
- Trophic feeds should be given as 1m1/kg every 2 hours.

Table 2. Advancements in enteral feeding: Slow increase

| Day of feeding | Volume per feed | Increment in feed volume (ml/kg/day) | Total feed volume for the day (ml/kg/day) |
|---|---|---|---|
| 1 | 1 ml/kg 2 hourly | 12 | 12 |
| 2 | 2ml/kg 2 hourly for 12 hours<br>3ml/kg 2 hourly for next 12 hours | 18 | 30 |
| 3 | 4ml/kg 2 hourly for 12 hours<br>5ml/kg 2 hourly for 12 hours | 24 | 54 |
| 4 | 6ml/kg 2 hourly for 12 hours<br>7ml/kg 2 hourly for 12 hours | 24 | 78 |
| 5 | 8ml/kg 2 hourly for 8 hours<br>9ml/kg 2 hourly for 8 hours<br>10ml/kg 2 hourly for 8 hours | 30 | 108 |
| 6 | 11ml/kg 2 hourly for 8 hours<br>12ml/kg 2 hourly for 8hours<br>13ml/kg 2 hourly for 8 hours | 36 | 144 |
| 7 | 14ml/kg 2 hourly for 8 hours | 32 | 168 |

Notes:

**High risk infants: Slow advancement in enteral feed volumes**

- Infants < 28 weeks gestation (up to 27 weeks + 6 days), or
- Birth weight < 2ndcentile, or Infants with evidence of significant perinatal asphyxia

• Tropic feeds at volume of 1 ml/kg 2 hourly (as in Day of feeding 1) should be continued until it is safe to advance enteral feed volumes.
• Feeds can be given when UAC/UVC are in situ.
• Feeds increment per feed is always by 1m/kg.
• Feed increments are every 12 hours from Day of feeding 2 to 4 and then every 8 hours.
• In breast milk fed infants, once the infants has achieved 150-180 ml/kg/day feed volumes (between day of feeds 6 and 7), consider adding breast milk fortifier. For those on preterm formula, increase feed volumes over 150m1/kg/day if indicated due to slow growth. At 150-180ml/kg/d volume, breast milk with added fortifier or preterm infant formula should be sufficient to meet the preterm infants' nutritional requirement. Continue parenteral nutrition and reduce volume of parenteral nutrition when enteral feed volumes exceed 70 ml/kg/day (day of feed 4-5) or the combined

fluid volume intake exceeds 150m1/kg/day unless higher fluid volumes are needed for other clinical indications.

Table 3. Advancements in enteral feeding: Fast increase

| Day of feeding | Volume per feed | Increment in feed volume (ml/kg/day) | Total feed volume for the day (ml/kg/day) |
|---|---|---|---|
| 1 | 1 ml/kg 2 hourly | 12 | 12 |
| 2 | 2ml/kg 2 hourly for 8 hours<br>3ml/kg 2 hourly for 8hours<br>4ml/kg 2 hourly for 8 hours | 30 | 42 |
| 3 | 5ml/kg 2 hourly for 8 hours<br>6ml/kg 2 hourly for 8hours<br>7ml/kg 2 hourly for 8 hours | 30 | 72 |
| 4 | 8ml/kg 2 hourly for 8 hours<br>9ml/kg 2 hourly for 8 hours<br>10ml/kg 2 hourly for 8 hours | 36 | 108 |
| 5 | 11ml/kg 2 hourly for 8 hours<br>12ml/kg 2 hourly for 8 hours<br>13ml/kg 2 hourly for 8 hours | 36 | 144 |
| 6 | 14ml/kg 2 hourly | 24 | 168 |

Notes:

**Moderate-low risk of NEC: Fast advancement in enteral feed volumes**

- Infants ≥28 weeks gestation at birth
- Birth weight ≥2ndcentile

- Tropic feeds at volume of 1 ml/kg 2 hourly (as in Day of feeding 1) should be continued until it is safe to advance enteral feed volumes.
- Feeds can be given when UAC/UVC are in situ.
- Feeds increment per feed is always by lm/kg.
- Feed increments are every 12 hours from Day of feeding 2 to 4 and then every 8 hours.
- In breast milk fed infants, once the infant has achieved 150-180 ml/kg/day feed volumes (between day of feeds 6 and 7), consider adding breast milk fortifier. For those on preterm formula, increase feed volumes over 150m1/kg/day if indicated due to slow growth. At 150m- 1801/kg/d volume, human breast milk with added

fortifier or preterm infant formula should be sufficient to meet the preterm infants' nutritional requirement.

• Continue parenteral nutrition and reduce volume of parenteral nutrition when enteral feed volumes exceed 70 ml/kg/day (day of feed 4-5) or the combined fluid volume intake exceeds 150m1/kg/day unless higher fluid volumes are needed for other clinical indications.

**Recommendation**:

• Increase enteral feeds by 1 ml/kg as per schedule as soon as infant is stable

**Feed intolerance:** Intolerance of feed is defined as:

- NG aspirates >2m1/hr in infants <750g or >3m1/hr in infants >750g (2)
- Significant abdominal distension
- Significant vomiting
- Bile-stained aspirates (green coloured aspirate)

Frequent stopping for enteral feeding should be avoided. If the infant has large volume aspirates only, consider reducing feed volume for 1-2 feeds and then increasing again. The decision to stop enteral feeds should be taken only where there are one or more of the above features present or if there are other concerns about NEC.

**Recommendation:**

• Monitor for feed intolerance but avoid frequent interruptions in enteral feeding

**<u>Fortification of maternal expressed breast milk</u>**

**Recommendation:**

• Addition of breast milk fortifier (BMF) to mother's expressed breast milk should be considered for the following infants once they establish feeds at 180 ml/kg/d of expressed breast milk

• Very low birth weight infants (birth weight < 1.5 kg)

• Infants with birth weight < 2kg who

- are IUGR (birth weight < 2thcentile for gestation)
- have poor weight gain on maximum tolerated feed volumes (not more than 180- 200 ml/kg/d or with conditions such as congenital heart diseases where fluid restriction may be required

**Vitamin supplementation in preterm infants**

- Preterm infants have a higher requirement for most vitamins due to premature delivery prior to the third trimester fetal accretion of nutrients resulting in low body stores.
- Vitamins should be supplemented in all preterm infants <34 weeks gestation at birth once full enteral feeds have been achieved (150 ml/kg/d). Preterm formula milk and breast milk fortifier have added multivitamins and hence the need for vitamin supplements varies with the milk the infant is receiving. Table 4 gives the dose of multivitamin supplementation required for different kinds of milks given to preterm infants.

**Recommendation:** Infants born at < 34 weeks gestation should receive daily multivitamins supplements.

**Indications for Milks and Supplements in NICU**

| Feed/Supplement | Indication |
|---|---|
| Expressed breast milk (EBM) | All infants |
| EBM + Nutriprem BMF | If <34w, bwt <1.5kg add BMF once tolerating 150ml/kg EBM |
| EBM + Nutriprem BMF | If <34w, bwt >1.5 <2kg add BMF if: Poor tolerance of volume<br>Poor weight gain<br>Serum urea <2mmol/l or steadily falling IUGR <9° at birth |
| Nutriprem Protein Supplement | Where additional protein only is required. New product in 2015 so indications not yet clearly defined |
| Nutriprem 1 | <34w, bwt < 2.0kg when insufficient or no EBM |
| SMA Gold Prem Pro | As per surgical guideline (D10) |
| Nutriprem 2<br><br>SMA Gold Prem 2 – an alternative brand available that can be used in the community | Nutrient enriched formula for infants who were <34w and <2kg at birth. Introduce before discharge or at 2.5kg. Can be prescribed as per ACBS by GP until 6m from EDD though should be changed to term formula once catch up growth is achieved. If before 6 months corrected iron and vitamins should be prescribed as per guidelines D5 & D8 |
| Term formula SMA First or C&G First | Used for term infants' weight > 2.0 kg and >34weeks |
| Infatrini */SMA High Energy* | Infants >37w on fluid restriction/high nutrient needs |

**Types of milk**

- Babies at any GA weighing less than 1.8 kg at birth: Nutriprem 1
- Babies less than 34 weeks GA and weighing between 1.8 kg and 2.5 Kg: Nutriprem 2
- Babies greater than 34 weeks GA and weighing over 1.8 kg at birth: ordinary formula C&G or SMA

**Indications for PN**

- When the newborn infant is unable to establish enteral feeds either through illness (RDS, necrotising enterocolitis), or immaturity or anomaly of the gastrointestinal system, and the prospect of significant volumes of enteral feeds is not envisaged in the short term (5 days)
- Extremely preterm (<30weeks), low birth weight infants (<1 kg) are severely nutritionally compromised after birth and are probable candidates for routine prescription of PN as it is highly unlikely that they will be receiving full enteral feeds within 5 days.
- In addition, PN is usually recommended for babies with severe intrauterine growth restriction (IUGR) where absent or reversed end diastolic flow is present on antenatal doppler scan. As rapid introduction of full enteral nutrition is probably not in their best interests and they are frequently intolerant of adequate enteral nutrition, these infants are at risk of prolonged sub-optimal nutrition and poor growth even if PN is introduced later.

**Neonatal PN regimens**

In order to ensure optimum nutrition within safe prescribing practices, a series of 4 ready- made bags of PN intended for use in NICU patients only have been designed and manufactured to cover the most likely scenarios found in neonatal intensive care.

**Starter Preterm Regimen PN** – ready made for use as soon as possible after birth for a maximum of 72 hours. Over long bank holiday weekends this regimen may be used for longer than 72 hours until Pharmacy Aseptic Services is open. Available in 160ml bags stored on the Neonatal Unit and cannot be modified. They are for central administration only.

Starter Preterm regimen PN is intended for use from birth in place of the historic practices of infusing 10% dextrose. Starter Preterm PN is similar to the aqueous component of the Preterm regimen but has no sodium, vitamins or trace minerals and less potassium, calcium and phosphate (see appendix 1). It should be prescribed according to individual fluid prescription. Lipid is not infused with Starter Preterm. Volumes over 80ml/kg/day are not intended and may cause glucose intolerance. Therefore, fluid requirements above this volume are better prescribed as 80ml/kg/day of Starter Preterm regimen PN and additional fluids as 5% dextrose (or 10% if extra glucose is required). Conversely, as some babies will receive only a

percentage of their fluid requirements as PN due to other infusions, efforts should be made to minimise the latter in order to maximise nutritional intake.

**Preterm Regimen PN** – should be used to follow on from Starter Preterm regimen PN and is commenced between 24-72 hours of age to provide optimum protein, glucose, electrolytes, minerals and a lipid infusion containing vitamins (may be longer over a bank holiday). The exact time between 24 and 72 hours at which Preterm regimen PN will commence will depend on the time of birth in relation to pharmacy supply of the prescribed Preterm regimen PN.

Preterm regimen PN provides full nutrition at ~100ml/kg of the aqueous bag and ~20ml/kg of lipid (fat) solution. Lipid should be prescribed at 2g/kg/day (12.5ml/kg/day) for 48 hours, and thereafter at 3g/kg/day (17.5ml/kg/day).

Infants who have not received starter pre-term regimen PN, and in whom preterm regimen PN is started after 48 hours, should have pre-term regimen PN at a maximum of 80mg/kg for the first 24 hours.

**Peripheral Regimen PN**– contains reduced amounts of protein, glucose, calcium and phosphate and is designed to reduce the osmotic and irritant effect on peripheral veins (see appendix 1). As this results in sub-optimal nutrient intake, Peripheral PN is only intended for short-term use with the agreement of the attending Consultant Neonatologist.

**Term Regimen PN**– designed for infants born >34 weeks. These bags are not routinely stocked in pharmacy but can be ordered for individual patients if appropriate. Patients should be maintained on Preterm regimen PN until the Term Regimen PN is available. In general, infants born prior to 34 weeks gestational age will not change to Term PN if they still require PN when they reach a corrected gestational age of 34 weeks as their requirements are still likely to be higher than babies born at this gestation.

Preterm, Peripheral and Term regimen PN should never be run at more than 120ml/kg/day. Additional fluids must be given as 5% dextrose (or more concentrated dextrose as guided by blood glucose levels) as appropriate.

## Nutritional Components

### Protein/Amino Acids/Nitrogen (N)

Aminoven Infant® 10% (Fresenius Kabi) is an amino acid solution specifically formulated to meet the protein requirements of neonates and infants, with a profile based on human milk protein. It contains 52% essential amino acids, other amino acids which are conditionally essential to neonates and preterm infants and a well-balanced pattern of non-essential amino acids. This product is unlicensed in the UK but licensed in Europe.

### Energy

Non-nitrogen energy is provided by glucose alone in the Starter Preterm regimen and glucose and fat (lipid) in an energy ratio of approximately 2:1 in Preterm and Term regimens. This ratio has been shown to promote good nitrogen retention. [3] Increasing carbohydrate and/or fat could provide more energy if required but advice must be taken from Neonatal Dietician or Neonatal PN Pharmacist. Any regimen requiring more or less carbohydrate would have to be out sourced (i.e. manufactured by another aseptic unit within the region). This would be at consultant request only. The Peripheral regimen has a lower ratio of glucose to fat due to the detrimental effect of glucose and beneficial effect of lipid on the patency of peripheral veins.

### Carbohydrate

Glucose is gradually increased as the administered fluid volumes increase. Starter Preterm contains 15% glucose and Preterm and Term regimens approximately 12.5% when prescribed in a total volume of 120ml/kg/day due to the addition of lipid. The Peripheral regimen has ~9% glucose concentration when prescribed with lipid.

### Fat (lipid)

Intralipid® 20% is the isotonic fat emulsion used and is a concentrated source of energy and the source of essential fatty acids in PN.
After infusion, the triglyceride portion is hydrolysed to free fatty acids. If the rate of infusion exceeds the rate of hydrolysis, triglyceride levels will rise. If the rate of

hydrolysis exceeds the rate of free fatty acid oxidation, plasma free fatty acids will rise. These displace bound bilirubin from albumin, which may be of some concern in infants with unconjugated hyperbilirubinaemia, though the concentration of free fatty acids likely to be a problem at any concentration of albumin is unknown.

The maximum amount of fat tolerated by preterm infants is difficult to determine. U.K. neonatal units set maximum amounts of fat infused at between 2-4g fat/kg/day depending on factors such as prematurity, birth weight and whether recipients are small for gestational age as all these factors are thought to affect tolerance due to lower levels of lipoprotein lipase [4]. Levels up to 3g/kg/day have been shown to be tolerated when infused over 24 hours [5, 6], though infants born weighing <1000g are less likely to tolerate even 3g/kg/d [7]. As the benefits of routine monitoring of triglycerides are not established, this is not undertaken.

The Preterm regimen PN increases from 2g fat/kg/day during the first 48 hours after lipid is first introduced to 3g fat/kg/day after 48 hours. The Term Regimen PN gives 3g fat/kg/day as soon as fluid intake reaches 120ml/kg. However, it is possible to adjust the fat independently of the rest of the nutritional components to achieve a slower increase and a higher or lower maximum level. There is evidence that intravenous fat is less well tolerated by the smaller, very premature infant, particularly if small for gestation [8]. However, the small for gestation age infant also has the greatest nutritional need. Increases to a maximum of 4g fat/kg/day may be required (at the request of the consultant) to achieve growth in some infants but should first be discussed with the Neonatal Pharmacist/Dietician. If fat prescription is increased beyond 3g/kg/day following such discussion, tolerance should be checked by measuring serum triglyceride concentration aiming for levels no higher than 2.8mmol/l.

**Vitamins**

A full range of water soluble and fat-soluble vitamins are added to the lipid portion of all regimens. Details of amounts added are given in Appendix 3.
If no lipid is prescribed, water-soluble, but not fat soluble, vitamins can be added to the aqueous solution. However, as full vitamins can be added to as little as 0.5g lipid/kg/day, this is rarely necessary as most infants should receive some lipid.

**Minerals**

Trace Minerals

A full range of trace minerals and electrolytes are added to give a complete feed. The trace mineral solution, Peditrace® is routinely added along with 0.2mmol/kg Mg as magnesium sulphate. Amounts added are given in Appendix 3. Although the manufacturers recommend that Peditrace® should not be added until renal function is established, this is rarely an issue in neonatal practice. Iron is not present in Peditrace® and is not routinely added to neonatal PN.

Calcium (Ca) & Phosphate ($PO_4$)

There is phosphate (as phospholipid) in both the Intralipid® and Vitlipid N Infant®. As this is thought to be bioavailable, the total phosphate figures in appendix 2 include that provided by 3g fat/kg/day (0.25mmol phosphate/kg). The amount provided by 2g fat/kg/day would be 0.18mmol phosphate/kg.

The ratio of calcium to phosphate is also important and should usually be no less than a molar ratio of 1:1 and this is provided when full lipid is prescribed [9]. Although higher amounts of these minerals may be possible without precipitation, more than 2.5mmol/kg Ca and 2.5mmol/kg $PO_4$ are rarely needed and should be discussed with the Neonatal Consultant, Neonatal Dietician or Neonatal PN Pharmacist. If Ca or $PO_4$ are modified from standard, or their ratio is altered, monitoring of serum concentrations must be increased to twice weekly (see Section 6.6 below). Total daily calcium intakes over 8.8mmol/day are not advised [10]. Note that when increasing phosphate an increase in PN sodium is usually required owing to the use of sodium glycerophosphate as the phosphate source. That is, for every 0.5mmol/kg/day increase in phosphate, it is usually necessary to increase the sodium by 1mmol/kg/day.

**Electrolytes**

Starter Preterm regimen PN, Preterm regimen PN, Term regimen PN and Peripheral regimen PN are pre-manufactured and the minimum nutrient levels are shown in appendix 1. Modifications to these should be kept to a minimum and can only be made in the Pharmacy Aseptic Unit. It is acknowledged that sick, preterm infants will have differing needs so a matrix has been agreed that allows prescription of more sodium, potassium, calcium and phosphate to be added by

Pharmacy Aseptic Unit only. Although serum electrolytes may need to be performed daily, it is not always necessary, or in fact helpful, to alter prescriptions daily.

The following should be considered before changing the sodium or potassium prescription:

- How long has any previous change been in effect?
- What is the trend or serial change in electrolytes rather than individual results?
- Are there other factors e.g. excess fluid losses or sodium from drug infusions?

Making gradual rather than large changes to avoid peaks and troughs If in doubt, discuss alterations with the NICU Attending Consultant

Sodium (Na)

Starter Preterm regimen PN does not contain sodium. The Preterm, Term and Peripheral regimens contain sodium as the glycerophosphate and the amount cannot be reduced. Hypernatraemia is not usually caused by excessive sodium intake but by inadequate hydration and through excessive water losses. In such cases, fluid administration should be increased. Sodium may need to be increased when sodium losses are high. Hyponatraemia may also be caused by use of excessively dilute fluid, inappropriate ADH (rarely) and excessive bowel losses.

Regimens have been shown to have solution stability up to 15 mmol Na/kg. Sodium intake is increased using sodium chloride and so will increase chloride load.

Potassium (K)

All Standard regimens contain some potassium (see appendix 1). In the Starter Preterm regimen this is in the form of potassium acid phosphate, in the Preterm regimen this is in the form of potassium acetate and in the Term and Peripheral regimens this is in the form of potassium chloride. Additional potassium prescribed to individual babies as part of these regimens will be provided as potassium chloride. Regimens have been tested for stability from 2.5-5mmol/kg/day.

**Table 1: Nutritional Composition of available PN regimens**
**(Standard amounts are shown with any agreed additions given in brackets)**

| Regimen | Starter preterm | | Preterm | Term | Peripheral |
|---|---|---|---|---|---|
| Administration | Central | | Central | Central | Peripheral |
| Volume (ml/kg/day) | 60 | 80 | Approx 120 | Approx 120 | Approx 120 |
| Nitrogen (g/kg/day) | 0.34 | 0.45 | 0.56 | 0.4 | 0.32 |
| Protein (g/kg/day) | 2.1 | 2.8 | 3.5 | 2.5 | 2 |
| Glucose (g/kg/day) | 9 | 12 | 15 | 15 | 11 |
| Glucose concentration (%) | 15 | 15 | 12.5 | 12.5 | 9 |
| Fat (g/kg/day) | - | - | 2 then 3[+] (0.5-3) | 3 (0.5-3) | 3 (0.5-3) |
| Energy (kcal/kg/day) | 44 | 59 | 94 then 104[+] | 100 | 82 |
| Sodium (mmol/kg/day) | - | - | 3.5 (max 15) | 3 (max 15) | 3 (max 15) |
| Potassium (mmol/kg/d) | 0.6 | 0.8 | 2.5 (max 5) | 2.5 (max 5) | 2.5 (max 4.5) |
| Calcium (mmol/kg/d) | 0.6 | 0.8 | 2 (max 2.5) | 1 (max 2.5) | 1 |
| Magnesium (mmol/kg/d) | 0.12 | 0.16 | 0.2 | 0.2 | 0.2 |
| Phosphate (mmol/kg/d) | 0.6 | 0.8 | *1.75 (max 2.25) | *0.75 (max 2.25) | *0.75 (max 2.25) |
| Chloride (mmol/kg/day) | Nil | Nil | Nil | 4.8 | 4.8 |

[+]Higher value is provided when 3g fat/kg/day prescribed after 48 hours of 2g fat/kg/day
*Additional phosphate is provided by the lipid (0.18mmol/kg/day with 2g fat/kg/day and 0.25mmol/kg/day with 3g fat/kg/day)

Trace elements and vitamins will be added in standard amounts to all (except starter preterm) PN unless requested otherwise.

## Nutritional Composition of PN Regimens When Prescribed at Regimen Standards

| Preterm Starter | /kg/day | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Volume** | **ml** | **10** | **20** | **30** | **40** | **50** | **60** | **70** | **80** |
| **Protein** | **g** | 0.35 | 0.7 | 1.05 | 1.4 | 1.75 | 2.1 | 2.45 | 2.8 |
| **Glucose*** | **g** | 1.5 | 3 | 4.5 | 6 | 7.5 | 9 | 10.5 | 12 |
| | **mg/kg/min** | 1.0 | 2.1 | 3.1 | 4.2 | 5.2 | 6.3 | 7.3 | 8.3 |
| **Fat** | **g** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Energy** | **Kcal** | 7 | 15 | 22 | 30 | 37 | 44 | 52 | 59 |
| **Na** | **mmol** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **K** | **mmol** | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 |
| **Ca** | **mmol** | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 |
| **Mg** | **mmol** | 0.02 | 0.04 | 0.06 | 0.08 | 0.1 | 0.12 | 0.14 | 0.16 |
| **P** | **mmol** | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 |

* Minimum expected glucose requirement – 4-6 mg/kg/min (5.8 – 8.6g/kg/day)

| Preterm (with either 2 / 3g fat/kg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | /kg/day | | | | | | | | |
| **Volume** | **ml** | **40** | **50** | **60** | **80** | **90** | **100** | **110** | **120** |
| **Protein** | **g** | 1.2 | 1.5 | 1.8 | 2.3 | 2.6 | 2.9 | 3.2 | 3.5 |
| **Glucose*** | **g** | 5 | 6.3 | 7.5 | 10 | 11.3 | 12.5 | 13.8 | 15 |
| | **mg/kg/min** | 3.5 | 4.3 | 5.2 | 6.9 | 7.8 | 8.7 | 9.5 | 10.4 |
| **Fat** | **g** | 0.7/1 | 0.8/1.25 | 1/1.5 | 1.3/2 | 1.5/2.25 | 1.7/2.5 | 1.8/2.75 | 2/3 |
| **Energy** | **Kcal** | 31/35 | 39/43 | 47/52 | 63/69 | 71/78 | 78/87 | 86/95 | 94/104 |
| **Na** | **mmol** | 1.2 | 1.5 | 1.8 | 2.3 | 2.6 | 2.9 | 3.2 | 3.5 |
| **K** | **mmol** | 0.8 | 1.0 | 1.3 | 1.7 | 1.9 | 2.1 | 2.3 | 2.5 |
| **Ca** | **mmol** | 0.7 | 0.8 | 1.0 | 1.3 | 1.5 | 1.7 | 1.8 | 2.0 |
| **Mg** | **mmol** | 0.07 | 0.08 | 0.1 | 0.13 | 0.15 | 0.17 | 0.18 | 0.2 |
| **P** | **mmol** | 0.7 | 0.8 | 1.0 | 1.3 | 1.5 | 1.7 | 1.8 | 2.0 |

| Term | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | /kg/day | | | | | | | | |
| **Volume** | **ml** | **40** | **50** | **60** | **80** | **90** | **100** | **110** | **120** |
| **Protein** | **g** | 0.8 | 1 | 1.3 | 1.7 | 1.9 | 2.1 | 2.3 | 2.5 |
| **Glucose*** | **g** | 5 | 6.3 | 7.5 | 10 | 11.3 | 12.5 | 13.8 | 15 |
| | **mg/kg/min** | 3.5 | 4.3 | 5.2 | 6.9 | 7.8 | 8.7 | 9.5 | 10.4 |
| **Fat** | **g** | 1 | 1.25 | 1.5 | 2 | 2.25 | 2.5 | 2.75 | 3 |
| **Energy** | **Kcal** | 33 | 42 | 50 | 67 | 75 | 83 | 92 | 100 |
| **Na** | **mmol** | 1 | 1.3 | 1.5 | 2 | 2.3 | 2.5 | 2.8 | 3 |
| **K** | **mmol** | 0.8 | 1 | 1.3 | 1.7 | 1.9 | 2.1 | 2.3 | 2.5 |
| **Ca** | **mmol** | 0.3 | 0.4 | 0.5 | 0.7 | 0.8 | 0.8 | 0.9 | 1 |
| **Mg** | **mmol** | 0.07 | 0.08 | 0.1 | 0.13 | 0.15 | 0.17 | 0.18 | 0.2 |
| **P** | **mmol** | 0.3 | 0.4 | 0.5 | 0.7 | 0.8 | 0.8 | 0.9 | 1 |

| Peripheral | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | /kg/day | | | | | | | | |
| **Volume** | **ml** | **40** | **50** | **60** | **80** | **90** | **100** | **110** | **120** |
| **Protein** | **g** | 0.7 | 0.8 | 1 | 1.3 | 1.5 | 1.7 | 1.8 | 2 |
| **Glucose*** | **g** | 3.7 | 4.6 | 5.5 | 7.3 | 8.3 | 9.2 | 10.1 | 11 |
| | **mg/kg/min** | 2.5 | 3.2 | 3.8 | 5.1 | 5.7 | 6.4 | 7 | 7.6 |
| **Fat** | **g** | 1 | 1.25 | 1.5 | 2 | 2.25 | 2.5 | 2.75 | 3 |
| **Energy** | **Kcal** | 27 | 34 | 41 | 55 | 62 | 68 | 75 | 82 |
| **Na** | **mmol** | 1 | 1.3 | 1.5 | 2 | 2.3 | 2.5 | 2.8 | 3 |
| **K** | **mmol** | 0.8 | 1 | 1.3 | 1.7 | 1.9 | 2.1 | 2.3 | 2.5 |
| **Ca** | **mmol** | 0.3 | 0.4 | 0.5 | 0.7 | 0.8 | 0.8 | 0.9 | 1 |
| **Mg** | **mmol** | 0.07 | 0.08 | 0.1 | 0.13 | 0.15 | 0.17 | 0.18 | 0.2 |
| **P** | **mmol** | 0.3 | 0.4 | 0.5 | 0.7 | 0.8 | 0.8 | 0.9 | 1 |

Derby Hospitals NHS
NHS Foundation Trust

## Starter Preterm PN Prescription

**Neonatal Starter Preterm regimen Parenteral Nutrition Prescription and Administration Record**

*Affix Patient Hospital Sticker Here*
Patient name:
Date of Birth:
Address:

Hospital Number:

Date: _____

Dosing weight: _____

Consultant: _____

PRESCRIPTION BASED ON:

| **Major Nutrients:** | | **Per 60ml/kg** | **Per 80ml/kg** |
|---|---|---|---|
| Protein | g/kg | 2.1 | 2.8 |
| Glucose | g/kg | 9 | 12 |
| Fat | g/kg | 0 | 0 |
| Sodium | mmol/kg | 0 | 0 |
| Potassium | mmol/kg | 0.6 | 0.8 |
| Calcium | mmol/kg | 0.6 | 0.8 |
| Phosphate | mmol/kg | 0.6 | 0.8 |
| Magnesium | mmol/kg | 0.12 | 0.16 |
| Total Energy | kcal/kg | 44 | 59 |

**For administration via a CENTRAL LINE ONLY for up to 72 hours after birth (may be longer over bank holiday weekend)**

- **No additions can be made to the bags.**
- **For single use only – discard remainder**
- **Each bag may be used for up to 48 hours**
- **The giving set and associated lines may be used for up to 48 hours**

**Volume Starter Preterm PN Prescribed = _____ ml/kg/day up to a maximum 80ml/kg/day**
Any extra fluid to be given as glucose 5% (or glucose 10% if blood glucose is low)

**Prescriber's signature: _____ Print Name: _____**

**FOR NURSING STAFF USE:**

| **Starter Preterm Bag** | **Batch number** | **Expiry date** | **Rate set (ml/hr)** | **Signed by** | **Checked by** | **Time** |
|---|---|---|---|---|---|---|
| | | | | | | |

**Shaded boxes above and flow rate must be completed before administration**

Derby Hospitals NHS
NHS Foundation Trust

**Chart for calculation and recording of Neonatal Parenteral Nutrition (PN) flow rates**

Date _____ Dosing weight _____kg

*Affix Patient Hospital Sticker Here*
Patient name:
Date of Birth:
Address:

Hospital Number:

1. Calculate starting lipid rate = ……..ml/hr
   (Step 1 overleaf)

2. Calculate starting protein/glucose rate = ……m/hr
   (Step 2/3 overleaf)

3. Calculate any rate changes and document below (step 2/3/4 overleaf):

| Total PN allowance (ml/kg/day) | Total infusions other than PN (ml/kg/day) | Enteral feed rate (mls per 2 hours) | New protein/glucose rate (ml/hr) | New lipid rate (ml/hr) | Rate changed | | |
|---|---|---|---|---|---|---|---|
| | | | | | 1st checker Sign | 2nd Checker Sign | Time |
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**Use a new chart for each new bag of PN**

## Appendix 6: Sample proforma for data collection and intakes calculation

### Nutrition and Growth in Preterm Infants

**Proforma for data collection**

| Patient details | |
|---|---|
| Study number | |
| Date of birth | |
| Sex | |
| Time of birth | |
| Gestation age | |
| Birth weight | |

| Diagnosis | Yes/No | Grade/severity |
|---|---|---|
| NEC (Grade) | | |
| IVH (grade) | | |
| PVL | | |
| Late onset sepsis | | |
| Chronic lung disease | | |
| ROP | | |

Yes
No

Suspected NE Grade 1
Proven NEC Grade 2
Advanced NE Grade 3
Advance NEC Grade 4

Culture prove In supplemental o Did not need LASER
Clinically susp In supplemental o Needed LASER

| | |
|---|---|
| Time of start of daily nursing charts | |
| Time of birth in complete hours | |

Duration of Day 1 24

| | | | | glucose solutions | | | | | PN | | | Other fluids | enteral feeds | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day of life | Working Body Weight | Actual Body Weight | | Volume of 5% glucose | Volume of 10% glucose | Volume of 12.5% glucose | Volume of 15% glucose | Volume of 20% glucose | Volume of PN | What is the concentration of glucose in this PN? | Volume of Lipid | Any other fluid (total volume in the duration) | Volume of EBM | Volume of Fortified EBM | Volume of Formula milk | Volume of Other Formula | Name of formula (if other) | starter PN | Parenteral nutrition given by (insert type of line) | | | |
| | kg | kg | | ml | ml | ml | ml | ml | ml | | ml | ml | ml | ml | ml | ml | | | Line | | | |
| Day 1 | | | | | | | | | | | | | | | | | | | | | | |
| Day 2 | | | | | | | | | | | | | | | | | | | | | | |
| Day 3 | | | | | | | | | | | | | | | | | | | | | | |
| Day 4 | | | | | | | | | | | | | | | | | | | | | | |
| Day 5 | | | | | | | | | | | | | | | | | | | | | | |
| Day 6 | | | | | | | | | | | | | | | | | | | | | | |
| Day 7 | | | | | | | | | | | | | | | | | | | | | | |
| Day 8 | | | | | | | | | | | | | | | | | | | | | | |
| Day 9 | | | | | | | | | | | | | | | | | | | | | | |
| Day 10 | | | | | | | | | | | | | | | | | | | | | | |
| Day 11 | | | | | | | | | | | | | | | | | | | | | | |
| Day 12 | | | | | | | | | | | | | | | | | | | | | | |
| Day 13 | | | | | | | | | | | | | | | | | | | | | | |
| Day 14 | | | | | | | | | | | | | | | | | | | | | | |

## Appendix 7: Research bulk calculator for growth Z-score

DO NOT ENTER DAYS OF AGE AS IT CAUSES CALCULATOR TO INCORRECTLY ROUND UP OR DOWN. IF YOU HAVE DAYS AND WEEKS OF AGE, AND YOU WISH TO USE THAT PRECISION, USE THE ACUTAL AGE CALCULATOR

**SGA is defined AT BIRTH ONLY as < 10th percentile for weight, LGA is > 90th percentile for weight

| Data Entry Cells - Boys | | | | | Calculated Cells - Boys | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | z-scores | | | | Percentiles | | |
| ID | Gest Age or Postmenstrual Age (22-49 completed wks)* | Weight 22-49 wks grams | Length 23-49 wks cm | HC 23-49 wks cm | SGA, AGA or LGA by weight at birth** | Weight Z | Length Z | Head circumference Z | Weight % | Length % | Head circumference % |
| | 22 | 695 | 31.6 | 22.2 | LGA | 2.1 | | | 98% | | |
| | 24 | 473 | 27.8 | 19.8 | SGA | -1.9 | -1.9 | -1.9 | 3% | 3% | 3% |
| | 36 | 2838 | 47.7 | 33.0 | AGA | 0.0 | 0.0 | 0.0 | 50% | 49% | 50% |
| | 49 | 2036 | 43.2 | 30.2 | SGA | -6.5 | -7.8 | -7.5 | 0% | 0% | 0% |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

www.ucalgary.ca/fenton

**Source:**

Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.
Paper is available free with open access from:
http://www.biomedcentral.com/1471-2431/13/59

Calculator written with assistance of Timothy P Stevens, MD, MPH, University of Rochester, Rochester, NY

* Data not available for length and head circumference of infants at 22 weeks gestation

**SGA is defined as < 10th percentile for weight, LGA is > 90th percentile for weight

**Procedure to calculate Z-scores and percentiles for your research database:**

1 Prepare your research data of age (in completed weeks of gestational age) with any size measuements you wish to use: weight (grams), Head circumference (centimeters), and/or Length
2 Copy up to 500 boy infants' data into the white columns, with an id number if you wish
3 This application will calculate girls exact Z-score and Percentile placement on the Fenton 2013 Preterm Growth Chart*.
4 Infant age must be reported as weeks, i.e. even weeks since the last menstural period or gestational age, between 22 and 49 weeks.
5 Copy and paste "Values" the resulting Z-scores and Percentiles into your database to retain your calculations

**Version 6** - includes SD23 correction for extreme weight z-scores, to improve accuracy of extreme values. While assessment revealed minimal differences with the SD23 correction, we wanted to follow the WHO's lead to provide the most accurate extreme z-scores as possible [1]. Head circumference and length were normally distributed throughout these charts so no corection was needed.

**Reference**

WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006 p 302
http://www.who.int/childgrowth/standards/technical_report/en/

DO NOT ENTER DAYS OF AGE AS IT CAUSES CALCULATOR TO INCORRECTLY ROUND UP OR DOWN. IF YOU HAVE DAYS AND WEEKS OF AGE, AND YOU WISH TO USE THAT PRECISION, USE THE ACUTAL AGE CALCULATOR

**SGA is defined AT BIRTH ONLY as < 10th percentile for weight, LGA is > 90th percentile for weight

| Data Entry Cells - Girls | | | | | Calculated Cells Girls | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | z-scores | | | | Percentiles | | |
| ID | Gest Age or Postmenstrual Age (22-49 completed wks)* | Weight 22-49 wks grams | Length 23-49 wks cm | HC 23-49 wks cm | SGA, AGA or LGA by weight at birth** | Weight Z | Length Z | Head circumference Z | Weight % | Length % | Head circumference % |
| | 22 | 649 | 30.9 | 19.5 | LGA | 1.7 | | | 96% | | |
| | 24 | 451 | 27.3 | 21.8 | SGA | -1.9 | -1.9 | 0.0 | 3% | 3% | 50% |
| | 49 | 2720 | 47.0 | 32.6 | SGA | -4.7 | -5.2 | -4.8 | 0% | 0% | 0% |
| | 36 | 1952 | 42.3 | 29.9 | SGA | -1.9 | -1.9 | -1.9 | 3% | 3% | 3% |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

www.ucalgary.ca/fenton

**Source:**

Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.

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2. Copy up to 500 girl infants' data into the white columns, with an id number if you wish
3. This application will calculate girls exact Z-score and Percentile placement on the Fenton 2013 Preterm Growth Chart*.
4. Infant age must be reported as weeks, i.e. even weeks since the last menstural period or gestational age, between 22 and 49 weeks.
5. Copy and paste "Values" the resulting Z-scores and Percentiles into your database to retain your calculations

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http://www.who.int/childgrowth/standards/technical_report/en/

## Appendix 8: Data requested from Neonatal Data Analysis Unit (NDAU)

A. Episode data

| Category | Category detail | Itemname |
|---|---|---|
| NNUEpisodes | Demographics and Birth Information (Baby) | Month of birth |
| NNUEpisodes | Demographics and Birth Information (Baby) | Year of birth |
| NNUEpisodes | Demographics and Birth Information (Baby) | Place of Birth NHS Code (Location of baby's birth) |
| NNUEpisodes | Demographics and Birth Information (Baby) | Birth weight (g) |
| NNUEpisodes | Demographics and Birth Information (Baby) | Gestation age in weeks |
| NNUEpisodes | Demographics and Birth Information (Baby) | Sex of the baby (phenotypic) |
| NNUEpisodes | Labour & Delivery | Drugs used during resuscitation |
| NNUEpisodes | Labour & Delivery | Was surfactant given during resuscitation? |
| NNUEpisodes | Admission details | Hospital baby admitted to |
| NNUEpisodes | Admission details | Clinical diagnosis at admission |
| NNUEpisodes | Admission details | Was Vitamin K indicator |
| NNUEpisodes | Admission details | Route of administration of Vitamin K |
| NNUEpisodes | Discharge details | Clinical diagnoses at discharge |
| NNUEpisodes | Discharge details | Discharge destination |

B. Daily care data

| Category | Category detail | Item Name |
|---|---|---|
| Daily | General information | General Information: Date of day of care anonymised |
| Daily | General information | General Information: Location of care |
| Daily | Respiratory | Respiration: Nitric oxide given |
| Daily | Respiratory | Respiration: Surfactant given today |
| Daily | Cardiovascular | Cardiovascular: IV infusion pulmonary vasodilator |
| Daily | Cardiovascular | Cardiovascular: Inotropes given |
| Daily | Cardiovascular | Cardiovascular: Prostaglandin infusion |
| Daily | Cardiovascular | Cardiovascular: Treatment for patent ductus arteriosus (PDA) |
| Daily | Blood transfusions | Transfusions: Blood products |
| Daily | Fluids and feeding | Fluids and feeding: Parenteral nutrition today (partial or total) |
| Daily | Fluids and feeding | Fluids and feeding: Intravenous glucose and electrolyte solutions |
| Daily | General information | General Information: Level of care (2011 definition) |
| Daily | Medication | Drugs given: Medications given on this day |

## Appendix 9: Additional results from Chapter 4

### Proportion of infants and characteristics of specific anti-reflux medications and feed thickener prescriptions

| Outcome | All infants n= 251,644 | Extreme preterm infants n=17,501 | Very preterm infants n=40,607 | Moderate and late preterm infants n= 193,536 |
|---|---|---|---|---|
| Number of infants who received Gaviscon, n(%) | 17491 (7.0) | 4,467 (25.5) | 7,757 (19.1) | 5,267 (2.7) |
| PMA at first prescription, median (IQR) | 34 (32-35) | 33 (30-36) | 33 (32-34) | 35 (34-36) |
| Number of days of prescription, median (IQR) | 13 (6-24) | 21 (10-37) | 15 (8-25) | 7 (4-12) |
| Number of infants who received Gaviscon at discharge, n(%) | 7423 (2.9) | 1,932 (11.0) | 3,239 (8.0) | 2,252 (1.2) |
| Number of infants who received H2RA, n(%) | 16115 (6.4) | 5,533 (31.6) | 6,426 (15.8) | 4,156 (2.1) |
| PMA at first prescription, median (IQR) | 33(30-35) | 30 (27-34) | 33 (31-34) | 35 (34-36) |
| Number of days of prescription, median (IQR) | 12 (5-26) | 17 (7-35) | 14 (6-26) | 7 (3-14) |
| Number of infants who received H2RA at discharge, n(%) | 6359 (2.5) | 2,034 (11.6) | 2,729 (6.7) | 1,596 (0.8) |
| Number of infants who received PPI, n(%) | 4279 (1.7) | 1,736 (9.9) | 1,744 (4.3) | 799 (0.4) |
| Number of infants who received Omeprazole, n(%) | 3882 (1.5) | 1,597 (9.1) | 1,547 (3.8) | 738 (0.4) |
| Number of infants who received Lansoprazole, n(%) | 479 (0.2) | 191 (1.1) | 216 (0.5) | 72 (0.0) |
| PMA at first prescription, median (IQR) | 35(33-38) | 35 (32-38) | 34 (33-36) | 36 (35-38) |
| Number of days of prescription, median (IQR) | 18 (9-33) | 24 (11-41) | 18 (9-29) | 12 (6-23) |
| Number of infants who received PPI at discharge, n(%) | 2771 (1.1) | 1,100 (6.3) | 1,165 (2.9) | 506 (0.3) |
| Number of infants who received Prokinetics, n(%) | 12865 (5.1) | 4,231 (24.2) | 5,503 (13.6) | 3,131 (1.6) |
| Number of infants who received Domperidone, n(%) | 10084 (4.0) | 3,370 (19.3) | 4,376 (10.8) | 2,338 (1.2) |

| | | | | |
|---|---|---|---|---|
| Number of infants who received Metoclopramide, n(%) | 8 (0.0) | 4 (0.0) | 1 (0.0) | 3 (0.0) |
| Number of infants who received Erythromycin, n(%) | 3648 (1.4) | 1,280 (7.3) | 1,468 (3.6) | 900 (0.5) |
| PMA at first prescription, median (IQR) | 33(31-35) | 31(29-35) | 32(31-34) | 35(34-36) |
| Number of days of prescription, median (IQR) | 17 (8-33) | 27 (12-48) | 19 (9-31) | 9 (5-15) |
| Number of infants who received Prokinetics at discharge, n(%) | 6164 (2.4) | 2,018 (11.5) | 2,716 (6.7) | 1,430 (0.7) |

PMA, postmenstrual age

**Proportion of infants with/without diagnosis of GORD and characteristics of specific anti-reflux medications and feed thickener prescriptions**

| Outcome | All infants n=251,644 | Diagnosed with GORD n=11,718 | No diagnosis of GORD n=239,926 |
|---|---|---|---|
| Number of infants receiving Gaviscon, n(%) | 17,491 (7.0) | 10,654 (4.4) | 6,837 (58.3) |
| Number of days of Gaviscon prescription, median (IQR) | 13 (6-24) | 18 (9-31) | 10 (5-20) |
| Number of infants receiving PPI, n(%) | 4,279 (1.7) | 1,743 (0.7) | 2,536 (21.6) |
| Number of days of PPI prescription, median (IQR) | 18 (9-33) | 21 (11-35) | 15 (7-28) |
| Number of infants receiving H2RA, n(%) | 16,115 (6.4) | 9,684 (4.0) | 6,431 (54.9) |
| Number of days of H2RA prescription, median (IQR) | 12 (5-26) | 18 (9-34) | 9 (4-20) |
| Number of infants receiving Prokinetics, n(%) | 12,865 (5.1) | 7,041 (2.9) | 5,824 (49.7) |
| Number of days of Prokinetics prescription, median (IQR) | 17 (8-33) | 24 (12-42) | 12 (6-24) |

## Appendix 10: Ethical approval for a new NNRD study

NHS
Health Research Authority

**Yorkshire & The Humber - South Yorkshire Research Ethics Committee**
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 1048091

03 March 2021

Dr Shalini Ojha
Clinical Associate Professor of Neonatology
Division of Graduate Entry Medicine
School of Medicine, University of Nottingham
DE22 3DT

Dear Dr Ojha

| | |
|---|---|
| **Study title:** | **An observational study of the association between anti-reflux medication use and adverse outcomes in preterm infants** |
| **REC reference:** | **21/YH/0055** |
| **Protocol number:** | **21008** |
| **IRAS project ID:** | **289926** |

The Research Ethics Committee (REC) reviewed the above application at the meeting held on 25 February 2021. Thank you for attending to discuss the application.

**Ethical opinion**

The members of the Committee present gave a **favourable ethical opinion** of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

| Number | Recommendation |
|---|---|
| 1 | The Committee recommended that the upper cap of participants (350,000) be reviewed to ensure that there were enough participants in the study. |

**Appendix 11: Questioannaire for Study 5 ( Clinicians and parents' GORD survey)**

# Gastro-oesophageal reflux in preterm infants

## Page 1: Introduction

Gastro-oesophageal reflux (GOR) is common in preterm infants and is often physiological. However, often it is associated with a range of troublesome signs/symptoms and is then called Gastro-oesophageal Reflux disease (GORD). There is a lot of uncertainty about the advantages and disadvantages of treating GORD in preterm infants.

We know that clinicians often prescribe medication but some clinicians first try non-pharmacological approaches such as feeding infants smaller volumes of milk more frequently or altering the position of the baby after feeds.

We are designing a clinical trial in **extremely and very preterm infants (<32+0 weeks gestational age) with GOR** and would like to explore your views and current practice.

We would be grateful if you could take a few minutes to complete our short survey.

Thanks in advance.

REFLUX (Reviewing use of anti-reflux medicines in preterm infants) Study group

## Page 2: Diagnosis

1. Which of the following do you consider to be signs/symptoms related to GORD in extremely and very preterm infants? (tick all that apply)

- ☐ Frequent regurgitation
- ☐ Frequent vomiting
- ☐ Gagging or choking
- ☐ Back arching or head extension
- ☐ Irritability or fussing
- ☐ Facial grimacing or pain after feeds
- ☐ Refusal to feed
- ☐ Hiccups
- ☐ Apnoea (any time)
- ☐ Desaturation (any time)
- ☐ Bradycardia (any time)
- ☐ Apnoea (during or after feeds)
- ☐ Desaturations (during or after feeds)
- ☐ Bradycardia (during or after feeds)
- ☐ Increased oxygen requirment
- ☐ Stridor
- ☐ Aspiration pneumonia
- ☐ Other

1.a. If you selected Other, please specify:

2. In your usual clinical practice, which tests do you use to diagnose GORD? (tick all that apply)

- ☐ No test, clinical diagnosis only
- ☐ No test, but use response to non-pharmacological management as a diagnostic strategy
- ☐ No test, but use response to pharmacological management as a diagnostic strategy

- [ ] Lower oesophageal pH monitoring
- [ ] Multichannel intra-oesophageal impedance (MII) monitoring
- [ ] Upper GI contrast
- [ ] Other

2.a. If you selected Other, please specify:

2.b. If you use pharmacological management to make a diagnosis of GORD, how long do you continue to assess the effect?

- ○ 2-5 days
- ○ one week
- ○ 1-2 weeks
- ○ >2 weeks
- ○ Other

2.b.i. If you selected Other, please specify:

## Page 3: Management of GORD

3. What strategies do you use to manage extremely and very preterm infants with GORD?

- ○ None, it is a self-resolving condition
- ○ Non-pharmacological management such as reduced feed volume, positioning
- ○ Pharmacological management (i.e. anti-reflux medication)
- ○ Trial of non-pharmacological management followed by pharmacological management (i.e anti-reflux medications)
- ○ Other

4. Which non-pharmacological strategies do you use to manage GORD? Tick all that apply

- ☐ None
- ☐ Head-up angle
- ☐ Head-up angle with upright position
- ☐ Car seat placement
- ☐ Left lateral position after feeds
- ☐ Prone position after feeds
- ☐ Reducing feed volumes by reducing total milk intake
- ☐ Reducing feed volumes by increasing the frequency of feeds
- ☐ Continuous intragastric feeding
- ☐ Continuous transpyloric feeding
- ☐ Feed thickeners such as starch or xanthan gum such as Carobel or Nutilis
- ☐ Other

4.a. If you selected Other, please specify:

5. Which pharmacological strategies do you use to manage GORD? Tick all that apply

- [ ] None
- [ ] Feed thickener with antacid such as Gaviscon
- [ ] Prokinetics such as Metoclopramide or Domperidone
- [ ] Histamine-2 receptor blockers (H2RA) such as Ranitidine
- [ ] Proton pump inhibitors (PPI) such as Omeprazole
- [ ] Other

5.a. If you selected Other, please specify:

6. If you use pharmacological treatments to treat GORD, how long do you continue the treatment usually?

- ○ 1-2 weeks
- ○ 2-4 weeks
- ○ 4-8 weeks
- ○ Until hospital discharge
- ○ Continue after discharge
- ○ Other

6.a. If you selected Other, please specify:

## Page 4: Clinical question

7. If you are caring for an extremely or very preterm infant with signs and symptoms of GOR that you think might require treatment, would you agree to enrol them into a clinical trial that would randomise the infants to either i) **Intervention group: Non-pharmacological management** (e.g. positioning, feed frequency) for a period of time to monitor if symptoms resolve (after which pharmacological management could be used if required/preferred) OR ii) **Control group: Pharmacological management**?

- ○ Yes
- ○ No

7.a. If no, why not?:

8. If you agree to participate in such a trial, in the intervention arm, how long would you agree to wait before considering starting treatment?

- ○ 3 days
- ○ 5 days
- ○ 7 days
- ○ 10 days
- ○ 14 days
- ○ Other

8.a. If you selected Other, please specify:

8.b. We are considering an outcome of **reduction in medication use.** What would you consider a meaningful reduction in use of medication for GOR?

- ○ <7 days

- 7 days
- 8 days
- 10 days
- 12 days
- 14 days
- >14 days
- Other

*8.b.i.* If you selected Other, please specify:

*9.* We are focussing on **extremely** and **very** preterm infants (born at <32 weeks) with signs/symptoms of GOR in the trial. How many infants who meet this criteria do you think you see each month at your hospital? (please estimate)

*10.* If you have any other views on the management of GOR in extremely or very preterm infants that you would like to share, please feel free to comment here:

## Page 5: About you

*11.* Are you a

- ○ Consultant Neonatologist/Paediatrician
- ○ Trainee in Neonatology/Paediatrics
- ○ Advanced Neonatal Nurse Practitioner
- ○ Nurse
- ○ Allied Health Professional
- ○ Other

*11.a.* If you selected Other, please specify:

*12.* What is the designation of the neonatal unit that you currently work in?

- ○ Level 1: Special Care Baby Unit
- ○ Level 2: Local Neonatal Unit
- ○ Level 3: Neonatal Intensive Care Unit

*13.* If funded, would you be interested in your unit participating in a randomised clinical trial in this area?

- ○ Yes
- ○ No

*14.* If yes, please give your hospital name and email address

More info

| | Email address | Hospital name |
|---|---|---|

# REFLUX Study parents survey

## Parents' views on reflux in premature babies

Babies born early often take some time learning to feed. They can be sick or posset after feeds. These features are sometimes linked to a problem called "gastro-oesophageal reflux" (also commonly called reflux) where contents of the stomach can come back into the gullet or food pipe. It's usually harmless and babies grow out of it as they mature. Many premature babies with symptoms of reflux are given medicine although research shows that babies get better even when they are not treated with medicines. Some of these medicines have been linked to other, more significant problems such as serious infection and a life-threatening bowel condition called necrotising enterocolitis (NEC). We have looked at data from many neonatal units in the UK which suggests that premature babies might be being "over-treated" with medicines for reflux. Currently, doctors aren't sure what the most effective way of treating babies like this is.

We are designing a national research study to find out the best way of caring for babies with reflux and to investigate if babies are being over-treated. We would like to compare the medicines currently used with other "non-medicine" techniques. These methods might include close monitoring of symptoms, giving the baby smaller (but more frequent) amounts of milk and putting the baby in different positions after any type of feed.

We plan to have two groups of babies: in one group babies would be cared for using the "non-medicine" techniques and in the other they'd receive medicine. We will monitor babies' symptoms every day for two weeks. After two weeks, babies in both groups (medicine & non-medicine) can be treated differently if the healthcare professionals and parents would like to try something else. Once the baby is discharged home, we will then compare the two groups and look at whether there were any differences in the babies' symptoms and the amount of medicine received.

It's really important to us that **parents of premature babies** are involved in helping us design our studies. Especially aspects such as how to approach parents, how

acceptable the care pathways are and what outcomes matter most to them. Therefore, before we complete the study design, we would like to know what parents think. We are particularly interested in the views of parents whose babies were born **before 32 weeks of gestation.** We would be very grateful, therefore, if you could take a few minutes to answer a few, short questions. Your responses are and will remain anonymous. All views (positive and negative) and opinions are hugely valuable to us. Your responses will help us design the best possible study in this area.

***You do not need to give any personal details - all responses are anonymous.***

Thank you in advance for your help.

Shalini Ojha
Clinical Associate Professor in Neonatal Medicine

Eleanor Mitchell
Assistant Professor of Clinical Trials

On behalf of the REFLUX Study group

Please click 'Next' to begin the questionnaire.

## Screening Question

Are you the parent of a baby who was born prematurely, i.e. before 37+0 weeks of gestation?

- ○ Yes
- ○ No

## About your baby

If you are the parent of more than one infant who was born prematurely, please answer the following question for the baby who was born the **most prematurely.**

How many weeks was your baby born at? (Tick one choice only)

- ○ <28 weeks
- ○ 28-31 weeks
- ○ 32-37 weeks

Was your baby diagnosed with **gastro-oesophageal reflux (GOR)** whilst in hospital? (Tick one choice only)

- ○ Yes
- ○ No
- ○ Don't remember

## About the proposed research study

We would like you imagine a scenario. Your baby has been born prematurely and is currently on the Neonatal Unit in hospital. You are told by the doctor that your baby is showing some signs of reflux, such as being sick frequently, not putting on weight, being unsettled or having some breathing problems.

You are invited to include your baby in a research study comparing two ways of treating their symptoms:

1) your baby is prescribed the usual reflux medicines used

or

2) your baby is cared for using other techniques such as increasing the frequency of feeds but reducing the amount of milk and putting babies on their sides after feeds.

At the time of the invitation to take part in the study, you are provided with all the information about both ways of treating your baby (including the possible risks and benefits). The information will also explain that premature babies might currently be being "over-treated" with reflux medicine and that doctors aren't sure what the best way to treat babies like this is. After two weeks, the baby can be treated differently (with or without medicine) if the healthcare professionals and parents would like to do so.

Based on the scenario above, we would like you to answer the following questions:

On a scale of 0-10, how comfortable would you feel about your baby **not** initially being given medicine for their reflux symptoms?

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Extremely uncomfortable | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | Extremely comfortable |

On a scale of 0-10, how comfortable would you feel about your baby initially being given medicine for their reflux symptoms?

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Extremely uncomfortable | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | Extremely comfortable |

Do you have a strong preference for how your baby's reflux symptoms should be treated? (Tick one choice only)

- ○ Yes - Treat with reflux medicines
- ○ Yes - Treat without reflux medicines initially
- ○ No - Don't have a preference

Why would you prefer for your baby to be treated with reflux medicines initially?

Why would you prefer for your baby to be treated without reflux medicines initially?

If you agreed for your baby to take part, a computer would decide which treatment option your baby will follow. You or your doctor could not choose at this stage. This is to make it a fair comparison. The computer chosen treatment (with or without reflux medicines) would be given for 2 weeks, after which you and your doctor could decide if you want to continue with the computer chosen treatment or change.

On a scale of 0-10 (0 being extremely uncomfortable, 10 being extremely comfortable) how comfortable would you feel about your baby's treatment being chosen by the computer?

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Extremely uncomfortable | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | Extremely comfortable |

We would collect data on your baby's symptoms whilst they are in the hospital. We would also send some questionnaires to you at home after your baby has been discharged to find out how they are doing a few weeks/months later. Would you be happy to agree to this?

- ○ Yes
- ○ No

If no, why not?

In theory, would you be willing for your baby to take part in the proposed study? *Please note that if you prefer for your baby not to take part, then your baby would be treated in the usual way that babies are treated at that hospital which would most likely be with medicines.*

- ○ Yes
- ○ No

If you answered no, then please indicate why not? (tick all that apply)

- ☐ I don't want my baby to take part in a research study
- ☐ I don't want the computer to decide how my baby should be treated
- ☐ I would prefer my baby to be treated with medicines
- ☐ I would prefer my baby to be treated without medicines
- ☐ I don't want to fill forms in
- ☐ Other

If you selected Other, please specify:

Please rank, in order of importance, what outcome of this research would be most important to you? (1 being least important, 4 being most important)

Please don't select more than 1 answer(s) per row.

Please don't select more than 1 answer(s) in any single column.

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Babies reflux symptoms are reduced overall | ☐ | ☐ | ☐ | ☐ |
| Babies have fewer days of reflux symptoms | ☐ | ☐ | ☐ | ☐ |
| Babies receive less reflux medicine overall | ☐ | ☐ | ☐ | ☐ |
| Babies receive fewer days of reflux medicine | ☐ | ☐ | ☐ | ☐ |

If you have any other suggested outcomes, please complete below:

If you had twin babies and both had reflux symptoms, do you have a preference about whether your babies are cared for in the same way? (tick one choice only)

- ○ I would prefer both babies to be cared for in the same way
- ○ I would prefer my babies to be cared for differently



Do you have any other comments about the study we are designing or about premature infants with gastro-oesophageal reflux in general?