UNIVERSIDADE DE LISBOA

Faculdade de Medicina

INSTITUTO POLITÉCNICO DE LISBOA

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Nutrition support of preterm infants in intensive care unit

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Orientadora

Professora Doutora Ana Catarina de Assunção Almeida Moreira

Dissertação especialmente elaborada para obtenção do grau de

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“A impressão desta dissertação foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 21 de Junho de 2020.’'

Resumo

Introdução: Os recém-nascidos prematuros são uma população propensa a deficiências nutricionais e ingestão insuficiente de energia. Quando a energia e os nutrientes não são suficientes, podem sofrer restrições de crescimento entre outras complicações. O objetivo deste estudo foi avaliar se RN prematuros internados em unidades de cuidados intensivos alcançaram as recomendações nutricionais pré-natais através da análise do ganho ponderal, ingestão de energia, proteína e aporte hídrico. Avaliamos igualmente se a adequação da ingestão de energia, proteína e fluidos foi suficiente para atingir as metas nutricionais. **Métodos:** Os dados foram recolhidos no Hospital Dona Estefânia no período de fevereiro de 2006 a outubro de 2008 em cinquenta e um prematuros com internamento> 4 semanas. Foi registado o sexo, a idade cronológica e o número de semanas de gestação, bem como dados do peso, e de ingestão de energia, proteína e fluidos. De acordo com as curvas de crescimento de Fenton foi analisado a adequação do ganho de peso semanal. A adequação da ingestão nutricional em energia, proteínas e fluídos foi determinada de acordo com as recomendações do European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. Utilizou-se o IBM SPSS Statistics para avaliar as correlações entre clínicas diferentes variáveis. **Resultados:** Encontraram-se deficiências de ingestão de energia, proteína e fluidos. Esta deficiências diminuíram com o tempo, verificando-se maior deficit nas primeiras semanas. Após a primeira semana, apenas um (1,96%) prematuro atingiu a meta de ganho de peso; na segunda semana e terceira semanas, 6 (11,76%) dos pretermos cumpriam as recomendações de ganho ponderal. Quanto maior (classificação de percentil de peso superior) e mais idade apresentava o prematuro, maior ganho ponderal apresentou. Verificaram-se correlações positivas entre o ganho de peso e a ingestão de energia, proteína e líquidos. **Conclusão:** É essencial garantir que os recém-nascidos prematuros ingiram nutrientes suficientes para atender às metas nutricionais garantindo a progessão ponderal adequada. Maior atenção ao cumprimento das necessidades deve ser dada ao recém-nascidos com menor tempo de gestação e mais baixo peso.

Palavras-chave: Prematuros; ganho de peso; ingestão de energia, proteína e fluidos

Abstract

Introduction: Preterm infants are prone to nutrient deficiencies and insufficient energy intake. When energy and nutrients are not enough, they will have growth restrictions and other complications. The purpose of this study is to evaluate if the preterm infants in preterm intensive care units achieved nutritional recommendations in energy, protein and fluids intake and to evaluate if they achieved the weight gain according to recommendations. We also evaluated the relations of energy, protein and fluids intake with nutritional goals achievement (weight gain). **Methods:** Data was collected from Hospital Dona Estefânia during February 2006 to October 2008 for fifty one preterm infants who stayed in hospital for at least four weeks. Their weight, energy, protein and fluids intake were collected and evaluated according to Fenton growth charts and guidelines from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. We used IBM SPSS Statistics to evaluate the correlations between clinical nutrition indexes. **Results:** Among the preterm infants we found deficiencies on energy, protein and fluids intake; the percentage of deficiencies of those nutritional intakes dropped by time. After the first week, only one (1.96 %) infant achieved the goal of recommended weight gain. On the second and third weeks, six (11.76%) preterm infants gained weight as recommendation. The bigger (higher weight percentile classification) and more mature infants were more likely to achieve weight gain. Positive correlations were observed between weight gain and the intake of energy/ protein/ fluids. **Conclusion:** It is essential for preterm infants to assure enough intake in energy, protein and fluids to meet the standard clinical nutritional goals such as weight gain. More attentions should be paid to assure adequate intake for the smaller and the more immature infants.

Key words: preterm infants; weight gain; energy, protein and fluids intake

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Lists of abbreviations

ELBW: extremely low birth weight
EN: enteral nutrition
EPT: extremely preterm infant
EUGR: extrauterine growth restriction
FFM: fat-free mass
GA: gestational age
HC: head circumference
HMF: human milk fortifier
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
PDA: patent ductus arteriosus
PGR: postnatal Growth Restriction
PMA: postmenstrual age
PN: parenteral nutrition
REE: resting energy expenditure
TPN: total parenteral nutrition
VLBW: very low birth weight

Nutrition support of preterm infants in intensive care unit

Chapter 1: Introduction of preterm infants

1.1. Definition, causes, physical features and complications:

Preterm infants are defined as new-borns who were born before 37 weeks of gestation. The gestational age is the number of weeks between the first day of the mother's last menstrual period and the day of delivery, and it can be corrected by early ultrasound scans. Preterm definition is further subdivided on basis of gestational age (GA): extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), moderate preterm (32 to 34 weeks) and late preterm (34 to 37 weeks). Even if late preterm babies may not look premature and may not need to be admitted to a neonatal intensive care unit (NICU), they are still at risk for more problems than full-term babies (1).

The World Health Organisation published in 2018 some of the main causes of preterm birth (2). The most common causes of preterm birth include multiple pregnancies, infections (such as urinary tract infections, sexually transmitted diseases, or infection of the uterus), and also chronic conditions such as diabetes and high blood pressure which can result in preeclampsia and eclampsia. There could also be a genetic influence (3).Apart from that, some other causes were described in literature, like cervical incompetence which is the cause of a weakened cervix or previous surgery involving the cervix (4) and maternal malnutrition, especially protein deficiency and/or vitamin E, folic acid deficiency (3).

Preterm infants present a set of physical characteristics. The physical features of preterm infants are as follow: small size and lower weight than term infants, large head relative to rest of the body, less fat mass under the skin, veins visible beneath the skin, scant hair, soft ears with little cartilage. For boys there is also the presence of small scrotum with few folds. Same of preterm girls can present labia majora not yet covering labia minora of the genitals. For both sexes, apart from the appearance, there can also be rapid breathing with brief pauses, apnea spells as well as weak, poorly coordinated sucking and swallowing reflexes and long periods of sleep (5).

Preterm infants may have very mild symptoms of premature birth, or may have more-obvious complications depending on the gestational age and mothers´ gravid health conditions. The prevalence of complications is high. One of the major complications with an underdeveloped brain is that preterm infants can have difficulty coordinating feeding and breathing (5). The parts of the brain that control reflexes involving the mouth and throat are immature, so premature new-borns may not be able to suck and swallow normally. As a consequence, they cannot or have difficulties with ingesting sufficient volumes of energy, protein, and micronutrition to assure catch-up growth rate and achieve a similar body composition to term infants. Related to the nutrition intake, another problem that presents in preterm infants is the underdeveloped digestive tract and liver (5). It is common to observe frequent episodes of vomiting and a high prevalence of intolerance for regular feedings, which worsen the nutritional status. Also, giving too much nutrition and giving it too quickly may lead to higher probability for the development of necrotizing enterocolitis (NEC). Besides the aforementioned nutritional complications, there is also the risk of frequent infections due to their immature immune systems. Sometimes antibiotics need to be used to cure this complication. However, very young infants who receive antibiotics are more at risk for developing necrotizing enterocolitis, sepsis, and even death than those are not exposed to antibiotics (6). Another complication that could happen among this population is electrolyte disturbance. The underdeveloped kidneys may have difficulty regulating the amount of salt and other electrolytes as well as water in the body (5). In NICU, preterm infants can be subjected to intravenous infusion to correct this situation. Because premature new-borns have feeding difficulties maintaining normal blood sugar levels, they are often treated with glucose solutions given by vein or given small, frequent oral feedings. Premature new-borns have a large skin surface area relative to their weight compared to full-term new-borns, also because they have less fat under the skin than term full-term infants, so they tend to lose heat rapidly and have difficulty maintaining normal body temperature (5). New-borns who have lower temperature have difficulty with weight-gain (5). Greater degrees of prematurity are associated with greater risks of serious and even life-threatening complications. Extremely premature new-borns tend to require a longer stay in the NICU until their organs can function well on their own and more autonomously meet nutritional need.

1.2 Prevalence of preterm infants

It is estimated that 15 million babies are born prematurely every year and the rate of preterm births is still rising (2). Preterm birth rates are increasing in almost all countries with reliable data which makes it a global problem. It is estimated that over 60% of preterm births occur in Africa and South Asia (7). The rate of preterm birth in Europe is rising steadily (8). From over 5 million births annually, the estimated preterm birth rate in Europe varies is from 5 to 10% (9).

New-born deaths, considered those in the first month of life, account for 40 per cent of all deaths among children under five years of age (7). Approximately one million babies die every year from complications of premature birth (7). Prematurity is the world's single biggest cause of new-born death, and is the second leading cause of all child deaths, after pneumonia (7). Meanwhile, because of better care from medical teams and with better living conditions than in the past, the rate of survival of preterm infants has increased significantly (10). But still many of the preterm babies who survive face a lifetime of disability. Historical data and new analyses show that deaths from preterm birth complications can be reduced by over three-quarters even without the availability of neonatal intensive care (7).

The imbalance in survival rates of preterm infants in the world is shocking. In a low-income environment, about half of new-borns born at 32 weeks die due to lack of feasible care, including warmth, breastfeeding support, and basic care for infections and dyspnoea (7). In high-income countries, almost all of these children can survive. Prematurity is an important public health priority in high-income countries. Besides, in high-income countries, improved care of the premature baby led to the development of neonatology as a discrete medical sub-specialty and the establishment of neonatal intensive care units (7). The use of poor technology in a middle-income environment has led to an increased burden of disability for preterm infants who survive in the neonatal period.

1.3 Characteristics of preterm infants

1.3.1 Pathophysiology of preterm infants

There are some major differences between term and preterm infants in pathophysiology like those findings in body temperature. Comparing to the term infants, the temperature regulation center of preterm infants is immature and the stability of body temperature is not stable. For them, there is less subcutaneous fat which leads to low heat storage capacity, and their brown adipose tissue supplying heat is immature as well. Meanwhile, their gastrointestinal tract is immature which makes them unable to take in enough energy to maintain body temperature (11).

Also, the respiratory system present differences. The respiratory center, vomiting reflex and cough reflex of preterm infants are relatively weak, prone to aspiration pneumonia. They are prone to have dyspnea, irregular apnea and cyanosis due to immaturity (12). More importantly, preterm infants born at a lower gestational age and/or with a greater degree of morbidity are most at risk of early feeding difficulties. Respiratory disease was identified as a particular risk factor. Mechanisms for feeding difficulty include immature or dysfunctional sucking skills and poor suck–swallow–breath coordination (12).

Another system showing differences is the circulatory system. Due to the incomplete development of the muscular layer of the small pulmonary arteries, if the arterial duct continues to open, the blood flow from the aorta to the pulmonary artery will increase, leading to pulmonary edema and hypoxia, constricting the pulmonary arterioles and causing pulmonary hypertension, and finally right heart failure (13).

Also common is for preterm infants to have immature digestive systems. Poor reflexes for sucking and swallowing put them at risk of aspiration pneumonia. The stomach volume is small and the food intake must be adapted to the reduced volume, which affects the needs of nutrition, calories and fluids. Infants with immature gastrointestinal function are at greater risk of developing a necrotizing enterocolitis (14). It is critical that health professionals pay careful attention to the proper intake of energy, protein, volume and micronutrition for preterm infants, avoiding complications and feeding intolerance.

One of the major situations that can lead to preterm infants' complications are related with the immaturity of their immune system. Most of the IgG immunoglobulin is obtained through the placenta at the end of pregnancy, as a consequence, preterm infants are more susceptible to infection than full-term infants. Additionally, the premature baby's immune system may have difficulty producing the necessary cells and proteins that make up the components of the system (15). For these reasons, preterm infants are susceptible to infection. Infection in a premature baby can come from many sources including the womb, the birth canal, or the Neonatal Intensive Care Unit (NICU) environment. They have a higher incidence of infections and sepsis (16). There may be lethargy, diminished responsiveness, fever, abnormalities with temperature control, abnormal breathing, and reduced circulation of the blood to the body (15).

The excretion system is frequently underdeveloped. Glomerular and tubular function and structure are relatively impaired at birth among both healthy and diseased preterm. As a result, the ability to recover electrolytes and glucose is hindered, and electrolyte disorders are prone to occur among preterm infants (17).

1.3.2 Metabolic imbalance in preterm infants

In general, preterm survivors are at a higher risk of growth and developmental disabilities compared to their term counterparts due to their special metabolic situation (18).

Preterm infants can have higher probability of being at a catabolic situation, and need to use they limited body stores and amino acids to maintain energy production at the expense of growth. Comparing to term infants, preterm infants have less energy stores when they are born. As most of the deposition of adipose tissue occurs in the final weeks of pregnancy, this poses a difficulty for the preterm infants, who will not have developed the required energy stores (19). Besides, preterm birth occurs during the third trimester of pregnancy when placental transfer of calcium, magnesium and phosphorus to the babies is particularly important to foster bone mineralization (20). As a consequence, preterm birth may have an increasing later risk for osteoporosis. Apart from that, study shows that preterm infants have less fat-free mass (FFM) than those born full-term (21). FFM is important cause it reflects protein accretion and indexes growth of organs, including the brain (22). The special body composition of preterm infants makes the nutritional care extremely unique and necessary while they stay in NICU.

Growth and development for preterm infants should be accelerated when energy and nutrients are available. In relation to intrauterine growth, the third three-month period of gestation is the most critical for fetal weight gain, and therefore, children born before full-term lose part of this weight gain (23). In addition, they go through an initial weight loss at birth, which on average reaches 15%, and is greater and more prolonged with lower gestational ages (23). As a consequence, the weights need to gain more than that of full-term infants to meet the standard weight for the same gestational age.

Therefore, the nutritional intake of energy, macro and micronutrients is of greater demand for preterm infants.

Besides, it is estimated that the resting energy expenditure (REE) is higher in preterm infants than term infants. Especially the lower gestational age they have, the higher REE they require (24).

Last but not least, increased metabolic demand can also occur in the premature neonate population. Though current understanding for the neonatal population is modest, study in adult and children shows that critical illness changes metabolism significantly by decreasing the rate of absorption and utilization of nutrients (25).

Due to those mentioned reasons, preterm infants require more careful nutritional supports than term infants even those born without complications.

1.3.3 Special nutritional needs for the preterm infants

The goal of nutrition support for preterm infant is to provide nutrients to meet the growth rate and body composition of the normal healthy fetus of the same gestational age in terms of weight, length, head circumference, organ size, tissue components including cell number and structure, concentrations of blood and tissue nutrients, and developmental outcomes (26). Nutrition is essential for growth, metabolism and immunity in preterm infants. Current markers of nutritional status include weight gain, length increase and head circumference according to recommendations (27).

There are some studies highlighting the importance of providing sufficient energy and protein intake for preterm infants. Protein and energy intakes during first week are associated with 18-month developmental outcomes in extremely low birth weight (ELBW) and extremely preterm infants (28). Besides, recent investigations on the effect of early postnatal nutrition indicated that the rate of weight gain in premature infants is influenced by the amount of calories given, whereas increase in length and head circumferences are influenced by the amount of protein in the diet (29).

Energy is extremely important for weight gain and neurodevelopment. Recommendations for energy intake are based on the assumption that growth and nutrient retention similar to intrauterine references are appropriate. For the preterm infants, less energy will compromise the growth standard and too much energy could have adverse outcomes as well (30). Failure to correct energy deficiency in premature infants may lead to adverse effects such as neurodevelopmental delay and negative long-term metabolic rate (25). The brain is a rapidly developing organ, which is responsible for 60% of total body's energy requirements (31). The neonatal brain is highly influenced by nutritional availability. Excessive energy will lead to more fat gain that will be synthesized and deposited in adipose tissue in growing preterm infants. In adults, such increased body adiposity is a risk factor for cardiovascular morbidity and metabolic syndrome (32). According to ESPGHAN a reasonable range of energy intake for healthy growing preterm infants with adequate protein intake is 110 to 135 kcal· kg^{-1} ·day^{-1} (33). Small-for-gestational age infants may need a higher energy intake than appropriate for gestational age infants (34).

As for the protein, an additional protein supply needs to be provided for early catch-up growth and compensating for the cumulative protein deficit developed during the first week of life. An increase in the protein-energy ratio is mandatory to improve the lean body mass accretion and to limit fat mass deposition. Apart from that, the quality of the provided protein may interfere with the recommended intake because the requirements of infant are not in proteins but in specific amino acids. Little is known about optimal intakes of these specific amino acids. A different composition of the proteins (and accordingly amino acids) administered may change the quantity of proteins required. Individual amino acids are important not just as building blocks for protein synthesis and net protein balance, but also as essential signalling molecules for normal cellular function (35). Perhaps most importantly, brain growth and later life cognitive function are directly related to protein intake during the neonatal period in preterm infants (35). It is recommended that 4.0 to 4.5 g · kg^{-1} · day^{-1} protein intake for infants up to 1000 g, and 3.5 to 4.0 g for infants from 1000 to 1800 g that will meet the needs of most preterm infants (33).

Water is the major component of the human body at any age and is an essential carrier for nutrients and metabolites. Within several days after birth, regardless of the amount of water intake, the urine output is increasing rapidly and frequently causes negative fluid balance. This is due to the reduction in the relatively excess volume of extracellular fluid; therefore, it is not necessary to raise the fluid supplement to correct the negative balance unless there are findings of suspected dehydration (36). On the contrary, postnatal intakes at the lower range is likely to minimise risk of long-term morbidity such as bronchopulmonary dysplasia and patent ductus arteriosus (33). It is recommended the intake of fluid is 135-200 mL ·kg^{-1} · day^{-1} (33).

Bone health is a critical concern in managing preterm infants. Key nutrients are calcium, vitamin D, and phosphorus. Rickets in preterm infants is almost always attributable to decreased total absorbed calcium and phosphorus (37). Calcium absorption depends on calcium and vitamin D intakes, and that calcium retention is additionally related to absorbed phosphorus. It is suggested that an intake of calcium 120 to 140mg $\cdot kg^{-1} \cdot day^{-1}$ decreases the risk of fractures, diminishes the clinical symptoms of osteopenia, and ensures appropriate mineralisation in very-low-birth-weight (VLBW) infants (33). With regard to consequences of intake too much calcium, hypercalciuria may lead to nephrocalcinosis that might adversely affect the renal function (38). Besides, the adequate phosphorus intake represents 65 to 90 mg · kg-1 ·day-1 of a highly absorbable phosphate source with a calcium to phosphorus ratio between 1.5 and 2.0 (33). Vitamin D is important for supporting a large number of physiological processes such as neuromuscular function and bone mineralisation. A vitamin D intake of 800 to 1000 IU/day (and not per kilogram) during the first months of life is recommended (33).

1.4 Consequences of malnutrition

1.4.1 One main result of undernutrition: Postnatal Growth Restriction or Extrauterine growth restriction

Extrauterine growth restriction (EUGR) is a situation defined as having a measured growth parameter (weight, length, or head circumference) lower than the 10th percentile of intrauterine growth expectation based on estimated postmenstrual age (PMA) at the time of hospital discharge (39). The incidence of EUGR increased with decreasing gestational age (GA) and decreasing birth weight. The more immature an infant is, the greater amount of nutrition per unit body weight is required. If not sufficient, EUGR happens. However, the immaturity of the digestion and metabolism function made it difficult for VLBW infants to obtain adequate nutrition so it is quite common that VLBW infants are diagnosed with EUGR. In addition, the more severe the respiratory or cardiac complications, the stricter water restrictions have to be taken, resulting in insufficient nutritional intake. Postnatal growth restriction (PGR) or EUGR has been identified as a major problem reflecting suboptimal nutrition of very preterm infants (40). A significant association existed between low protein and energy intake and reduced growth velocity (40). To achieve the nutritional goals, getting enough and proper amount of protein and energy intake is very important. Inadequate nutrition especially during the first weeks of life is considered largely responsible for EUGR or PGR (41) (36).

1.4.2 Consequences of malnutrition with impact on adult age

Many diseases and complications may happen due to malnutrition for preterm infants. Protein deprivation in preterm neonate restricts renal glomerular growth which in later life is associated with smaller than normal kidneys and hypertension (42). Also, poor nutrition is associated with poorer head growth. Persistent smaller head size results in poor psychomotor and mental skills, higher rates of cerebral palsy, and autism (43). Also impaired weight and growth in preterm infants are significantly associated with adverse neurodevelopmental outcomes in later life (44). It has been noted that malnutrition in the early postnatal phases in preterm infants results in lower verbal intelligence quotient (IQ) scores and impaired cognitive function in the long term (45) (46). Apart from that, preterm infants who do not get enough nutrients have higher possibility to get retinopathy of prematurity which may result in childhood blindness and vision impairment (47). Last, preterm infants are at risk for low bone mass and metabolic disease mainly due to calcium and phosphorus deficiency because they miss out the period of greatest mineral accretion that occurs during the last trimester of pregnancy and without sufficient intake after born (48).

1.5 Nutritional support in preterm infants

1.5.1 Type of nutrition support

Infants receive nutrition orally, enterally or via parenteral infusion, depending on gestational age and the unique clinical factors associated with each infant during the neonatal period. The majority of infants born after 34 weeks gestation without significant complications are mature enough to coordinate a suck, swallow, and breathe reflex, allowing them to be fed by mouth (49). Infants born prior to this gestational age typically begin parenteral nutrition within the first 24 hours of life (49). Enteral nutrition is initiated and advanced based on the degree of prematurity and clinical condition of the infant, gradually replacing parenteral nutrition. Meanwhile, NEC is the dominant argument for postponing enteral feeding.

【Parenteral nutrition (PN)】

The achievement of adequate nutritional intakes in preterm infants during the first few weeks of life is challenging, and one potential strategy to address this task is the use of early parenteral nutrition initiated soon after birth. Preterm infants are often not able to tolerate volumes of oral feeds that will provide adequate daily requirements for growth within the first week or two of life, therefore parenteral nutrition is often required. Several recent reports demonstrated that adequate protein and energy intakes from PN can significantly improve postnatal growth in very preterm infants (45) (50). It can also reduce NEC (51).

Given the likelihood of accumulated energy deficits and the potential needs for catch-up growth in preterm infants, most practitioners aim for at least 120 kcal/kg per day to facilitate maximal protein accretion (52). Infants receiving PN tend to need lower intakes because splanchnic tissue metabolism and stool losses are much lower than during enteral feeding (52).

There are some adverse outcomes with total parenteral nutrition (TPN). The risk of sepsis and other complications during total parenteral nutrition (TPN) is high (51). TPN also provides certain important nutrients less effectively, notably vitamin A, glutamine, calcium, and phosphorus (51). Prolonged parenteral nutrition easily causes cholestasis or hepatic dysfunction, which is known as parenteral nutrition associated cholestasis (53).

【Enteral nutrition (EN)】

There are three ways to provide enteral feeding: trophic feeding, bolus feeding or continuous feeding. Trophic feeding is the provision of milk feeds in sub-nutritional quantities (10–15 mL/kg/day) for a predetermined period. It has also been termed “minimal enteral nutrition” and “gut priming” (51). It reduced the period before full tolerance of enteral feeds and shortened hospital stay without increasing incidence of NEC (20) as well as significantly less likely to develop sepsis (51). Also, tropic feeding is associated with a decreased duration of parenteral nutrition (54).

Due to the lack of ability of preterm infants to coordinate suckling, swallowing, and breathing, tube feeding is necessary for most infants less than 1500 g to ensure sufficient feeding tolerance, to support optimal growth and to reduce the risk of aspiration (55). Therefore, feeding by orogastric or nasogastric tube using either continuous or intermittent bolus delivery of formula or human milk is common practice for these infants. According to the literature, continuous nutrition could be preferred in smaller infants (as those with a birthweight below 1250 g) or hemodynamically impaired infants; in stable growing infants nutrition can be administered intermittently as in healthy term infants (55). Besides, bolus feeding is associated with an increase in splanchnic oxygenation, which might reflect an increase in blood flow in the mesenteric region. On the other hand, continuous feeding is associated with a significant decrease in splanchnic oxygenation (56).

There are several types of milk and formulas provided by enteral routine considering maternal milk with or without fortifier and different types of infant formulas.

Human milk is the first choice for the preterm infants. There are significant host defence benefits from mothers'own milk for preterm infants. The use of human milk was associated with a significantly reduced incidence of NEC (51). Besides, in a comparison, babies fed on human milk tolerated feeds at an earlier postnatal stage than formula fed babies, allowing TPN to be withdrawn considerably sooner (57). Despite the many advantages of human milk for reducing infection and promoting better neurodevelopmental outcomes in preterm infants, preterm infants fed unsupplemented human milk do not grow at the intrauterine rate (58). Unsupplemented mature human milk provides an insufficient quantity of protein to support the growth and lean body mass accretion of very preterm infants (36). The concentrations of calcium and phosphorus in human milk are also significantly below that necessary to attain in utero levels of bone mineralization (59). The calorie, protein, and minerals should be increased by adding human milk fortifier (HMF) to human milk. There is no definite guideline for when to start HMF. Some centers fortify as soon as a total of 25 mL/day is used, some fortify when feeding amount reaches 100 mL/ kg/day, and others at full volume feeding (36). Human milk calories are usually calculated at 67.7 kcal/100 mL. Initially, one packet is added to 50 mL (75 kcal/100 mL) for 1-2 days, then one packet to 25 mL (81 kcal/100 mL). This method of human milk fortification will achieve the nutrient content at the target of 3.6 g/kg protein if used on 120 kcal/ kg, which is compatible with the recently recommended P/E ratio at 3.6 g/120 kcal for very premature infants (36). Apart from that, for those infants who are discharged while still receiving expressed breast milk, fortification is a more practical continuing option and may be especially important for infants who receive donated breast milk, which contains lower nutrient levels than maternal expressed breast milk.

Preterm infant formulas can be another choice for preterm infants when human milk is not available. There are several types: Similac Special Care family 20®, Similac

Special Care family 24®, and Similac Special Care family 30® (36). Similac Special Care 20® has energy similar to breast milk (67.6 kcal/100 mL). It is protein-enriched (2.0 g/ 100 mL) and also enriched with minerals, vitamins, and trace elements to support intrauterine nutrient accretion rates (36). Similac Special Care 24 and 30 are higher energy formulas of 81 kcal/100 mL and 101 kcal/100 mL that may be used to increase the nutrient density of the feeding regimens without increasing the fluid volume or as a ready-to-feed formula (36). The higher energy formula has increased fat and lower carbohydrate content to reduce the increased osmolarity. It is recommended that the high energy formula not to be used as a ready-to-feed formula early on when feeds are being established in VLBW infants and that it be used with caution later on. In practice, we initially use a preterm infant formula of 67.6 kcal/100 ml (36). Under some special conditions, such as chronic lung disease, patent ductus arteriosus (PDA), or congenital heart disease with heart failure, where the infants require a higher nutrition under fluid restriction, we use the high energy formula. As for Similac Special Care 30, when it is mixed 1:1 with human milk, it provides 84 kcal/100 mL to meet the energy needs of most preterm infants and it can be suitable for use as a human milk fortifier (36). Besides, it has increased calcium and phosphorus content of human milk to support growing bones.

1.5.2 Early aggressive nutrition

The purpose of early aggressive nutrition is to reduce the cumulative caloric and protein deficits in acute stage to a minimal degree and hence to prevent EUGR and associated abnormal cognitive and neurodevelopmental outcomes (60). This strategy involves initiating early parenteral and enteral nutrition, especially initiation of an amino acid infusion providing about 3 g protein/kg/day within hours of birth, initiation of a lipid emulsion of 0.5-1.0 g lipids/kg/ day within 24 to 30 hours of birth, and initiation of minimal enteral feedings with initially small amounts (10-20 mL/kg/day), and then advancing, within the first 5 days of life (36).

As for the fluids, it starts from 60 to 80 mL/kg/day, gradually increase 10 to 20 mL/kg/d (according to the change in birth weight, serum Na^+, urine amount and circulatory status) to 120-150 mL/kg/d at day 7 (including IV and feeding amount) (36). Within several days after birth, regardless of the amount of fluids intake, the urine output is increasing rapidly and frequently causes negative fluid balance. This is due to the reduction in the relatively excess volume of extracellular fluid; therefore, it is not necessary to raise the fluid supplement to correct the negative balance unless there are findings of suspected dehydration. We have to be careful about the amount of fluids because excessive fluid loading will lead to patent ductus arteriosus and chronic lung disease in premature infants (61).

As regards the energy and protein, they should match to keep the proper energy/protein ratio to better use both things. The goal is 120 kcal/kg/d and protein 3.6 to 4.0 g/kg/d (36). In clinical situation, hospitals use parental way mostly for preterm infants which is IV amino acid (10%) 3 g/kg/d to be started within hours after birth, increase 0.5-1 g/kg/d until it reaches 3.6-4 g/kg/d (36).

Usually, human milk is initiated at 0.5 mL/kg on day one if possible (at least within 3-5 days), and advanced to 10-20 mL/kg/d as tolerated. The goal of feeding amount is 120-150 mL/kg/day (36).

1.6 Justification for this research

Preterm infants are special and need careful care. Most of them are interned to NICU after birth until they meet the clinical standard to discharge. Insufficient amounts of nutrients, an imbalance of nutrients, or a poor biological state may stop premature infants from achieving their full growth potential. During their NICU time, it is critical to ensure sufficient nutrition to prepare them for discharge from the hospital and to assure optimal development. There are several clinical nutritional evaluations for the preterm infants including weight gain, head circumferences, length as example of anthropometric measurement. This study was focused on the weight gain as a dynamic metric change. Analysis of protein, energy and fluid intake are some of the most important measurements to perform during the hospital stay to assure their nutrition intake. In the following research, we analysed whether preterm infants got enough energy, protein and volume according to the recommendation. We also evaluated the weight gain comparing to recommendations based on the age and sex according to Fenton tables. We analysed associations between weight gain with energy, protein and volume.

Chapter 2: Research

2.1 Objectives

This research had major four objectives:

1. To assess if preterm infants in NICU gained weight according to guidelines.
2. To analyse associations between weight gain with gestational age and percentile of weight.
3. To assess if preterm infants in NICU got enough energy, protein and fluids based on recommendations.
4. To assessed associations between energy, protein and fluids intake and weight gain.

2.2 Study population

This was a random controlled trial of consecutively admitted neonates born with ≤ 33 weeks of gestational age and who had not been submitted to major surgery (48) . Infants with major congenital abnormalities, severe central nervous system disorders, and bone and/or muscular diseases were not included. A minimal of four week's permanency in intensive care unit was needed. Nighty five preterm infants from Hospital Dona Estefânia were enrolled during February 2006 to October 2008. Of those, forty-four preterm infants were excluded because they were discharged or transferred to other hospitals before the end of study period. At the end, fifty-one preterm infants met the inclusion criteria and were evaluated.

2.3 Ethics

Data collection was approved by the ethics committee of Hospital Dona Estefânia and informed parental consent was obtained. Only participants who gave consent were analysed. Data was computerized in a database ensuring confidentiality and anonymity of participants. Registration of race and ethnicity is not permitted under Portuguese law.

This is a post analysis, to pursue a secondary objective of a previous published study (48).

2.4 Methodology

Neonate's data were recorded and analysed for a four weeks period. According to gestational age and sex, neonates born weight were classified in percentiles of 2013 Fenton Preterm Growth Chart (62). Gestational age was calculated from the mothers' last menstrual period, corrected by early obstetric ultrasound.

During hospital staying Infants weight was measured weekly from birth till discharge. Data was recorded by nutritionists.

Enteral and/or parenteral nutritional support was delivered according to protocol previously described (48). Patient's daily nutritional intake in fluid, energy and protein was estimated from the prescriptions, corrected with the records of the effectively delivered volumes of parenteral and enteral nutrition and fluids. The mean intake by week was then calculated to be compared with recommendations.

To evaluate if preterm infants gained weight according to recommendation, we calculated the amounts based on different ages, sex and Fenton percentile. We counted individually and calculated those numbers by percentages (real/recommended weight gain). Higher and equal than 100% meant they met the standard and lower than 100% meant the opposite.

To analyse associations between weight gain with gestational age and percentile of weight. We used ´weight gain comparison´ which was real/recommended weight gain to evaluate weight gain. We used SPSS to analysis the correlations between them.

To assess nutritional needs, we used the guidelines from the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. We used a reasonable range of energy intake for healthy growing preterm infants, with adequate protein intake, consider 110 to 135 kcal· kg-1 ·day-1 (33) according to the guideline. Protein intake recommendations are 4.0 to 4.5 g · kg-1 · day-1 for infants up to 1000 g and 3.5 to 4.0 g for infants from 1000 to 1800 g to assure the needs of most preterm infants (33). ESPGHAN also recommend amount of fluid intake to be 135-200 mL ·kg-1 · day-1 (33). These recommendations were compared with real preterm intake. To compare if preterm infants got enough energy, protein and fluid, we used data by percentage which was real/recommended intake. Lower than 100% meant insufficient intake and higher than 100% meant excessive intake.

To investigate the importance of energy, protein and fluids intake considering of weight gain. We used ´weight gain comparison´ which was real/recommended weight gain to evaluate weight gain. In addition, we used ´energy, protein and fluid comparison´ which was real/recommended to evaluate the correlation in SPSS.

2.5 Statistical Analysis

We analysed the Normality of continuous numerical variables. As appropriate, data were expressed as mean±standard deviation, minimum and maximum according to distribution. Spearman correlation was used to compare associations between variables when the data was not normally distributed. When Correlation coefficient was positive and P values <0.05, the correlations were considered significant. Statistical analysis was performed with IBM SPSS Statistics 26 and Microsoft Excel 2016.

2.6 Results:

Infant characteristics: The total number of patients enrolled in the study was fifty-one. Mean gestational age was 29.3±2.0weeks (minimum was 26 weeks and maximum was 33 weeks) and birth weight was 1209±359g (minimum was 420g and maximum was 1970g). Twenty-one (41.2%) are male and thirty (58.8%) are female.

According to by Fenton 2013 Preterm Growth Chart percentile classification, (Table 1), the majority (84.4%) of neonates were classify between 10th and 90th percentile.

Fenton percentile	Frequency	Percent (%)
<3rd	2	3.9
3rd-10th	5	9.8
10th-50th	19	37.3
50th-90th	24	47.1
90th-97th	1	2.0

Table1: Fenton classification by weight at birth

Analysing the amount of energy, protein and fluids intake during the four week's period study we verify from the first till the fourth week were respectively that the median total real energy intake 63.6±54.6 kcal, 117.4±60.8 kcal, 137.2±62.0 kcal and 158.2±62.3 kcal by day. Moreover, those preterm infants intook 1.8±1.7g, 3.4±1.8g, 3.8±1.8g and 4.5±1.7g/kg/day of protein during the four weeks study period. Regarding fluids, the mean intake was 143.3±62.7ml, 192.9±69.0ml, 202.7±67.0ml and 220.0±75.5ml.

Confronting real intake with recommendations of energy, protein and volume, we found that during the first week, only 3(5.9%) infants got enough energy, 22(43.1%) infants got enough fluids and only 2(3.9%) infants got enough protein. During the second week, 18(35.3%) infants got the recommended intake of energy, will regarding protein intake was according to recommendations in 9(17.6%) of patients. Meanwhile, only 2(3.9%) infants were bellow fluids intake recommendation. During the third week, 2(39.2%) infants got enough energy and 12(23.5%) infants got enough protein. Only 1(2.0%) infant did not get enough fluids. From the forth week, the last week of investigation, 29(56.9%) and 10(19.6%) infants got enough energy and protein respectively. While 3(5.9%) infants did not get recommended fluids intake. As time passed, the deficiency of energy and protein intake dropped. The similar occurred on the fluid's intake deficiency that drooped the first three weeks and in the last week almost kept the same record.

2.6.1 Adequacy of weight gain and association with percentile of weight and gestational age

Regarding nutritional status evaluation, after the first week, only 1(2.0 %) infant achieved the goal of weight gain. For the second week, 6(11.8%) met the standards. As for the third week, the same number, 6(11.8%) preterm infants gained weight as recommendation (Figure 1).

We analysed the correlation between percentile of weight and adequacy of weight gain. There were positive associations in weeks 2 and 3 (R=0.669; P=0.000 and R=0.462; P=0.001), meaning bigger (higher weight percentile) infants were those who gained more weight. For the first week, the association between percentile of weight and adequacy of weight gain did not reach statistical significance (R=0.208; P=0.144).

With respect to the correlation between gestational age and the adequacy of weight gain, there were significant positive correlations between them for the whole study period. From the first week to the third week, gestational age was found to be positively correlated with adequacy of weight gain (R=0.536; P=0.00, R=0.567; P=0.000 and R=0.532; P=0.000).

2.6.2 Associations of adequacy of weight gain with adequacy of energy, protein and fluids intake

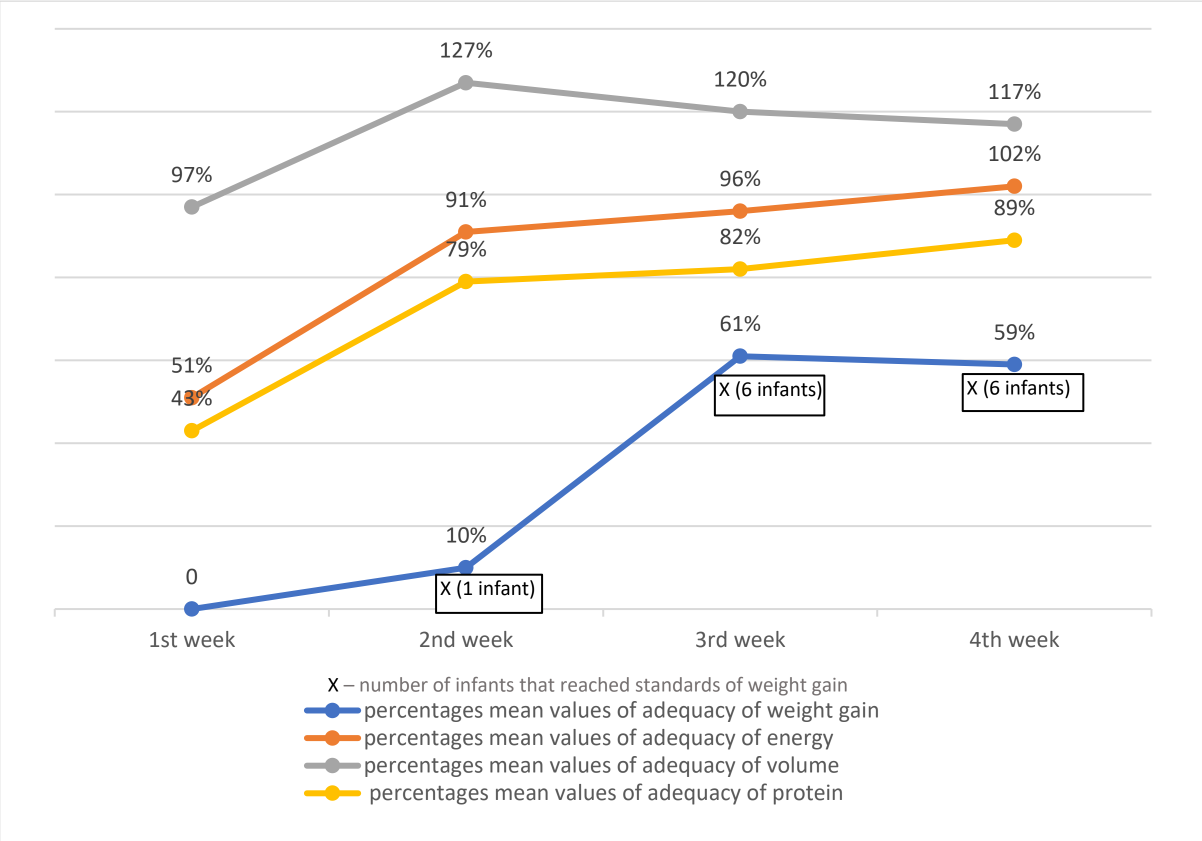
When comparing the adequacy of weight gain with adequacy of energy intake, for the first week, the adequacy of weight gain was found to be positively correlated with adequacy of energy intake (R=0.722; P=0.000). For the second week, the adequacy of weight gain had a significant association with adequacy of energy intake (R=0.340; P=0.015). For the third week there was no association with statistical significant (R=0.177; P=0.214).

For the association between the adequacy of weight gain and adequacy of fluid intake, we fund that for the first week, the adequacy of weight gain and adequacy of fluid intake were strongly correlated (R=0.705; P<0.000). For the second week, the correlation between them was found not to be statistically significant (R=-0.069; P=0.632). Results indicated an inverse association on the third week (R=-.102; P=0.478). The positive correlations showed that, as the adequacy of volume was reached, the more adequate the weight gain achieved. Conversely, in the 2nd and 3rd week correlation coefficient turned to be negative which meant that the more fluids a neonate got, the less weight they gained.

Furthermore, we analysed the relationships between the adequacy of weight gain and adequacy of protein intake. The correlation between the adequacy of weight gain and adequacy of protein intake was found to be statistically significant during the first week (R=0.746; P<0.000). For the second week and third week, there was no statistical correlation (R=0.248; P=0.079) and (R=0.100; P=0.485) respectively.

Associations of adequacy of weight gain, energy, protein and fluids intake are shown in Figure 1.

Figure1: Number of patients that reached the adequate weight gain and percentages mean values of adequacy of nutritional intake by week.



Comparing the adequacy of nutrition intake with adequacy of weight gain (Figure 1), it is clear that as energy, protein and volume increased, the weight gain raised. When the percentage of volume was over 100% which preterm infants overtook the fluids, they did not gained weight.

2.7 Discussion:

In the present study, we found that mean weekly weight gain was proportional to percentile of weight, that is, the larger the infants, the greater mean weight gain. In another study it was also demonstrated that mean daily weight gain velocities were proportional to birth weight, that is, the larger the infants, the greater the mean weight gain velocities (g/day) (64). In addition, we observed that mean weekly weight gain was proportional to gestational age. In other studies this might be as little as 5 grams a day for a tiny baby at 24 weeks, or 20 to 30 grams a day for a larger baby at 33 or more weeks (63). As the desired weight gain depends on the baby's size and gestational age, we found that bigger and older neonates gained more weight.

This study provided support for the hypothesis that increased energy intake leaded to increased weight gain in preterm infants, based on the finding of a similar study where energy intake on the 3rd and 7th days of life was positively correlated with weight growth velocity (65). In another study, the results provided evidence that energy intake during the first postnatal week is important in reducing the initial weight loss in EPT (extremely preterm) infants (66). In addition, we should notice that the importance of protein. If energy intake is not adequate, protein utilization is not efficient, which results in lower nitrogen retention (67). The energy is used only for fat deposition when energy is excess (67). Excess accretion of adipose tissue will lead to a situation that may have significant adverse long-term health outcomes (68). Hence, achieving nutritional goals like gaining weight, taking sufficient energy and but not overloaded amount plays an important role in future health.

Our data contributed to the assumption that preterm infants gained more weight by taking more protein and fluids during the first week. Two other studies indicated similar results revealing protein intake is of major importance for the first postnatal week for weight gain (65) (66). Those authors concluded that the rate of weight gain in premature infants is influenced by the amount of calories given, whereas gains in length and head circumferences are influenced by the amount of protein in the diet (69). Our study indicated the same results as there was no statistical association between adequacy of weight gain with protein and fluids intake for the second and third week. Therefore, to evaluate the impact of protein and fluids in nutritional status, it is better to use other body metrics. Additionally, excess fluid administration results in generalized edema and abnormalities of pulmonary function (70). Our study also indicated that excess fluid administration was inversely proportional to adequacy of weight gain, probably because these fluids aren’t only associated to nutrition intake but also as used as pharmacotherapy carrier. More studies that include other variables like pharmacotherapy are needed to confirm and explain this result.

This study was limited by several factors. The data from this study was collected in year 2006 to 2008. During that time, the nutritional recommendations were slightly different from recent ones, and the findings may not be generalizable to present neonatal care. Moreover, the dimension of study population was small.

In conclusion, the findings from this study suggest that bigger and older neonates gained more weight. Furthermore, they suggest that sufficient energy, protein and fluids intakes are important to achieve the nutritional goal like gaining weight. Therefore, healthcare professionals should direct efforts toward promoting and supporting nutrition according to guidelines. They should also pay more attentions to smaller and younger neonates.

Further researches need to focus on the issue that preterm infants with illness may need more specific nutrition like energy and protein. As far as we know, there are not enough studies that have been done with neonates considering the ones with disease. More studies are needed to evaluate the nutritional needs and the real administration of nutritional support.

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Appendix 1

Infants that achieved weight gain

number	age(weeks)	sex	Fenton	weight gain compare
1	30	male	10th-50th	129% and 152%
2	31	male	3rd-10th	115%
3	32	male	10th-50th	100%
4	33	female	10th-50th	143%
5	33	female	50th-90th	112%
6	33	female	50th-90th	130%
7	33	female	50th-90th	116%
8	33	female	10th-50th	100%
9	33	female	10th-50th	110%
10	34	female	50th-90th	120%
11	34	male	50th-90th	158%
12	34 and 35	male	50th-90th	118%

Anexos 1

Anexos 1.1 Fenton preterm growth chart for boys

Anexos 1.2 Fenton preterm growth chart for girls

Anexos 2

Anexos 2.1 Postnatal growth standards for preterm infants head circumference boys
Anexos 2.2 Postnatal growth standards for preterm infants head circumference girls
Anexos 2.3 Postnatal growth standards for preterm infants length boys
Anexos 2.4 Postnatal growth standards for preterm infants length girls
Anexos 2.5 Postnatal growth standards for preterm infants weight boys
Anexos 2.6 Postnatal growth standards for preterm infants weight girls