UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
DOCTORAL SCHOOL

DOCTORAL THESIS

PROTEIN INTAKE NUTRITIONAL RECOVERY OF PRETERM LOW WEIGHT AND VERY LOW BIRTH, NEONATAL PERIOD

PHD SUPERVISOR

PROF.UNIV.DR.POPESCU FLORICA

PHD STUDENT:

STOICĂNESCU EUGEN CRISTI

CRAIOVA

2018

CONTENTS

1. CURRENT STATE OF KNOWLEDGE .... Error! Bookmark not defined.

1.1 Newborn premature: definition, classification and short epidemiology Error! Bookmark not defined.

1.2 Neonatal complications selected at n.n. premature. 1

1.3 Nutrition of the newborn prematurely. 1

1.3.1 Enteric nutrition of the newborn prematurely. 2

1.3.1.1 Advantages of early minimal enteral nutrition (trophic or priming) 2

1.3.1.2 Nutritional needs at the n. premature. .. Error! Bookmark not defined.

1.3.2 Parental nutrition of premature newborn .... Error! Bookmark not defined.

2 OUR CONTRIBUTIONS .... Error! Bookmark not defined.

2.1 Objective .... Error! Bookmark not defined.

2.2 Material and method .... Error! Bookmark not defined.

2.3 Results 4

3 DISCUSSIONS .... Error! Bookmark not defined.

4 CONCLUSIONS .... Error! Bookmark not defined.

LIST OF ABBREVIATIONS

ELBW - extremely low birth weight
ELBWI - extremely low birth weight infants
PN – parenteral nutrition
TPN - total parenteral nutrition
SPN - standardized parenteral nutrition
IPN - individualized parenteral nutrition
EPN - Early Parenteral Nutrition (EPN)
LPN - Late Parenteral Nutrition
NICU: neonatal intensive care unit
VLBW: very low birth weight
SGA: small for gestational age
AA - amino acid
GA - gestational age
AAP - American Academy of Pediatrics
ASPEN - American Society for Parenteral and Enteral Nutrition
ESPGHAN - The European Society of Paediatric Gastroenterology, Hepatology and Nutrition
CSPEN - Pediatrics, Chinese Society of Parenteral and Enteral Nutrition
WHO World Health Organization
DHA - docosahexaenoic acid
RDA - recommended dietary allowance
LCT - long-chain triglycerides
MCT - medium-chain triglycerides
PUFA - polyusaturated fatty acids
RGO - rate of glucose oxidation
EFA- essential fatty acid
LC-PUFA - long chain PUFA
Gn – weight at birth

Keywords.

Prematurely, premature weighing less than 1500g, premature weighing less than 1000g, enteral nutrition, parenteral nutrition, protein intake, computerized program.

1. THE STATE OF KNOWLEDGE

1.1 Newborn premature: definition, classification and short epidemiology

Premature birth is the birth that occurs between 22 and 37 complete gestation weeks, resulting in a premature baby with signs of immaturity, body weight of 500-2499 gr and a 25-45 cm height. A premature birth can be accidental (spontaneous premature) or consequential to a medical decision (premature prematurity).

By premature baby is meant any newborn, regardless of birth weight, born before 37 weeks of gestation (less than 259 days).

Table 1. Classification of prematurity - After the International Classification of Diseases

Newborn prematurely	Gestational age	Weight at birth
Low weight (LBW)	VG<37 weeks	G.N.: 2499 – 1500 g
Very low weight (VLBW)	VG<32 weeks	G.N.: 1499 -1000 gt
Extremely small weight (ELBW)	VG <28 weeks	G.N.: 999 – 700 g
Incredibly small weight (ILBW)	VG <24 weeks	G.N. <700

The chance of survival varies with gestational age at birth: at 23 weeks the chance of survival is 17%; at 24 weeks the chance of survival is 39%; at 25 weeks the chance of survival is 50%; at 26 weeks the chance of survival is 80%; at 27 weeks the chance of survival is 90%; at 28-31 weeks the chance of survival is 90-95%; at 32 weeks or more many newborns can survive.

High mortality (measured by number of deaths per 1,000 live births) is found in: Angola 180; Sierra Leone 154; Afghanistan 152; Liberia 138; Nigeria 116. Low neonatal mortality was recorded in: Singapore 2.31; Bermuda 2.46; Sweden 2.75; Japan 2.79; Hong Kong 2.92; USA 6,30. Globally, in 2016, 2.6 million children died in the first month of life, 7,000 AD. (1 million deaths were on the first day of life and another 1 million in the next 6 days)

In 2011, the infant mortality rate registered in Romania (according to the National Institute of Statistics) was once again the highest in Europe (9.4 per 1,000 live births), with premature birth being the main cause. In Romania, over 20,000 children are born prematurely and with little birth each year, prematurity being one of the main causes of neonatal mortality.

1.1 Neonatal complications selected at n.n. premature.

Respiratory distress syndrome; chronic pulmonary disease; intracerebral haemorrhage; vulnerability to infection / sepsis; hyperbilirubinemia; gastroesophageal reflux; apnea of prematurity; anemia of prematurity; arterial canal persistence; necrotic enterocolitis; neonatal convulsions; retinopathy of prematurity.

1.2 Nutrition of the newborn prematurely.

According to many experts in neonatal nutrition, the target for premature infant feeding should be attaining a postnatal growth rate close to that of the normal fetus of the same gestational age. Restriction of growth is a significant problem because many studies have conclusively demonstrated that undernutrition, especially protein, at critical stages of development produces long-term short stature, organ failure and neural deficits of dendritic number and connections with negative cognitive outcomes.

Nutritional products used in premature neonatal nutrition are a complex amalgam of more than 40 macronutrients and micronutrients, each of which is necessary in an amount sufficient to have an increase in the healthy body. Deficiencies or excess of a macronutrient, such as protein, or micronutrient, like zinc, can diminish growth.

1.2.1.1 Enteral nutrition of the newborn prematurely.

The American Academy of Pediatrics (AAP) and the Nutrition Committee of the European Society of Pediatrics, Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended an energy intake of 105-130 kcal / kg / day and 110-135 kcal / kg / day for premature infants. Infants sometimes require increased caloric intake due to a higher increase in energy consumption during a disease. Thus, these recommended energy requirements may not be sufficient. Failure to provide adequate protein may have long-term adverse effects in premature infants. Each additional gram of protein intake for ELBW is associated with weight gain of 6.5 g / day and increase in head circumference with 0,4 cm / wk.

Although enteral nutrition can be administered via orogastric or transpirical probe, the immaturity of gastric emptying and slowed intestinal transit often exclude the use of enteral nutrition in the early days of prematurity.Avantajele alimentației enterale minime precoce (trofice sau priming).

Production of digestive hormones; digestive kinetics is modified by reduced intake per person; reducing the number of days required to achieve full dietary intake; reducing signs of digestive intolerance; increased weight gain with decreased hospitalization duration; better mineralization of the bone; the risks of cholestasis associated with parenteral nutrition; reduces the risk of sepsis. The American Society for Parenteral and Enteral Nutrition suggested in 2009 that ELBW and VLBW may benefit from minimal enteral nutrition starting at 0.5-1 ml / kg / day and increasing very slowly to 20 ml / kg / day. Current data suggest that early minimal nutrition should be initiated within the first 2 days of life and advanced by 30 ml / kg / day in infants ≥ 1,000 g. The amount of food increases gradually regardless of gastric residue or if gastric emptying improves.

1.2.1.2 Nutritive needs of n.n. premature.

The calorie requirement varies between 95-165 cal / Kgc / day according to the European Society of Gastroenterology and Nutrition. Most calories come from the metabolism of proteins, carbohydrates and lipids. The CSPEN Guide recommends in the case of n.n. premature 110-135 cal / Kgc / day by enteral nutrition, and in premature babies of extremely low weight 150 cal / Kgc / day.

Required protein: is 3 - 3.5 g / Kgc / day (15% of the calorie requirement). The protein source for the premature newborn is the mother's own milk that is richer in protein than the term newborn in which whey proteins predominate. It contains more cysteine and taurine used for neurological and retinal development. After gestational age at birth, the protein requirement is 4.4. g / kg / day at a GA of 26 to 30 weeks, 3.6-4 g / kg / day at a GA of 30-36 weeks and 3.0-3.4 g / kg / day at a GA 36-40 weeks.

Table 2. Current recommendation of nutrients for enteral nutrition n.n. premature.

	Greutatea la naştere	Consumul de proteine (g/kg/zi)	Raţia de energie (kcal/kg/zi)
American Academy of Pediatrics 1985	800-1200 g	4,0	105-130
	1200-1800 g	3,5	105-130
Canadian Pediatric Society 1995	<1000 g	3,5-4,0	105-135
	>1000 g	3,0-3,6	105-135
"Creștere" - stabilă din punct de vedere clinic și câștig de greutate -2005	ELBW	3,8-4,4	130-150
	VLBW	3,4-4,2	110-130
European Society for Paediatric Gastroenterology, Hepatology and Nutrition	<1000 g	4,0-4,5	110-135
	1000-1800 g	3,5-4,0	110-135
From “Protein requirements of very low birth weight infants,”	500-700 g	4,0	105
	700-900 g	4,0	118
	900 -1200 g	4,0	119
	1200 -1500 g	3,9	127
	1500 – 1800 g	3,6	128
	1800 -2200 g	3,4	131
Ghidul CSPEN /2013	<1000g	4 -4,5	150
	1000-1800g	3,5 – 4,0	Raport

			proteine/energie 3,2-4,1g/100 kcal

1.2.2 Parental nutrition of premature newborn

Parenteral nutrition is indicated at: n.n. premature babies with birth weight less than 1000 g; birth weight 1000-1500 g and expected not to be significantly fed in the next 3 or more days; birth weight greater than 1500 g and it is anticipated that it is not on significant food for 5 or more days; surgical conditions in neonates: necrotizing enterocolitis, gastroschisis, omphalocele, tracheo-esophageal fistula, intestinal atresia, bowel rotation, short bowel syndrome and ileus meconial.

Mode of administration of parenteral nutrition: PN can be achieved through a peripheral and / or central vein. The peripheral vein produces a short-term PN and a long-lasting central one.

The peripheral vein - the percutaneous intradermal injection of the silastic catheter through the peripheral vein tolerates the osmolarity of the solutions from 700 to 1000 mOsm / l. The maximum glucose concentration that can be administered on the peripheral vein is 12.5% and the central vein 25%. The amino acid concentration should not exceed 3.5% due to the risk of thrombophlebitis. The infusion solution should not contain calcium because of the risk of extravasation with serious complications, cutaneous necrosis. Usually this pathway is used for short-term nutritional support. Requires frequent change of vessel (maximum 2 to 3 days).Vena centrală (confirmare radiologică): prin cateter de silastic radioopac cu diametrul de 1,3 mm plasat în vena cavă superioară, plasat chirurgical prin jugulara internă sau externă; această cale de administrare este folosită la pacienţii care necesită suport nutriţional de lungă durată, uzual TPN. Soluţiile hiperosmolare sunt mai bine tolerate. Risc infecţios mai mare, măsuri de asepsie mai dure (mănuşi sterile, mască). Complicaţii: tromboze, embolii, sepsis.

Parenteral nutrition may be discontinued when the infant receives ≥100 to 120 cc / kg of enteral nutrition or when it requires less than 25 cc / kg / day of PN.

Early Parenteral Nutrition (EPN – nutriţie parenterală precoce) şi *Late Parenteral Nutrition* (LPN – nutriţie parenterală tardivă). EPN sunt definite prin administrarea de proteine în primele 24 ore (EPN) şi LPN după 24 ore.

For most preterm newborns, PN administration within the first 24 hours from birth and gradually increasing during the first week of life, including the suggested amounts of 3.5-4 g / kg / day of protein, 3-4 g / kg / day of lipids and 90-110 kcal / kg / day of calories, can slow down weight loss after birth and raise growth limits.

Pediatric amino acid solutions are recommended. On the first day of life, 1.5 to 2 g / kg / day (n.n. without abnormal kidney function) is administered and increased to 3 g / kg / day at n.n. and 3.5-4 g / kg / day in preterm. Nonprotective nitrogen / calorie is 1 g / 100 -200 kcal.

Ibrahim et al indicates premature infants tolerate 3.5 g / kg / day with a positive nitrogen balance on the first day of life. Doses of 3.3 g / kg / day to 3.9 g / kg / day are also well tolerated.

Total Aggressive Parenteral Nutrition: Pregnancy Aggressive Total Parental Nutrition (PN) is defined when the total of 4g / kg / day of amino acids is administered by standardized PN in neonates in the first week of life. Currently, aggressive nutrition of n.n. prematurely not only through the early administration of NP but of all nutrition.

Complications encountered during NP are: hyper / hypoglycaemia; electrolyte disturbances (Na, K, Cl, Ca, P, Mg) (hypo- or hyper-); acidosis; hyperchloraemic; azotemia: hyperammonemia, aminoacidemia; lipid disorders (hyperlipidemia, essential fatty acid deficiency); trace element deficiency; vitamin deficiency;

intrahepatic cholestasis; Infectious - septicemia; endocarditis; osteomyelitis; septic embolism; nephritis; infection at catheter insertion. Technical - Catheter: Disconnection of the tubing, malposition, thromboembolism, infection, parvovirus infusion with necrosis; Cord: arrhythmia (for the central catheter); Venoas: embolism, thrombophlebitis, perforation.

In conclusion, the principles of the practice of wounding must include:

1. Initial initiation of breast feeding enterococci 0.5 -1 ml / hr at start and gradual increase after tolerance
2. Aggressive PN as early as possible after birth;
3. Immediate introduction of lipid emulsion iv 0.5-1 g / kg / day, increasing gradually to 2-3g/kg/day, increasing the intestinal nutrition more quickly than the NP

2 OUR CONTRIBUTIONS

2.1 Objective

Determining the protein requirement for premature recovery of Gn under 1500, and making a predictive mathematical model of this need through a computer program.

2.2 Material and method

The retrospective statistical survey on 50 premature babies from 2015-2016, admitted to the Râmnicu Vâlcea Maternity and the Sibiu Maternity.

The inclusion criteria involved the absence of illnesses that inevitably evolved to death, or requiring transfer to other (ex surgery) or high energy-consuming sections, so that the common factor of the subjects was premature and premature complications that can be medically controlled . From the point of view of nutrition, as a criterion for inclusion, it was intended as a common factor: to initiate early (starting with the first day) feeding with breast milk and to maintain it throughout the hospitalization period. In all cases, intermittent gavage was used, with a frequency of 8 meals / day. Dried milk formula used: Alfare (one meal / day), fortifying - FM 85, protein supplement - Aptamil PS.

For parenteral nutrition, 10%, 20% Smoflipid, 10% and 5% Glucose Soil, Electrolites (NaCl 5.85%, 10% Gluconic Acid) were used as common preparations. The route of administration - the venous umbilical catheter.

In the database, the daily amount of enteral and parenteral protein was introduced, with the calculation of total daily intake and need. From day 14, data entry was performed at 14-day intervals (due to nutritional stability, preterm at this age being without exception, fed exclusively enterally). Transfusions, mechanical ventilation duration, prematurity complications (Premature Retinopathy, Anemia, Cerebral Ischemic Lesions, Sepsis, Ulceronecrotic Enterocolitis) were counted.

For statistical analysis of data, the software used was SPSS versus 13. As a statistical analysis tool, descriptive analysis (mean, standard deviation, minimum and maximum intervals), cluster analysis, ANOVA and student significance tests, Pearson correlations , Multiple Linear Regressions. The evolutionary differences in different precursor groups, the differences in protein nutrition tolerance, the effect of enteteral and parenteral nutrition on the premature development and the consequences on prematurity complications were investigated.

2.3 Results

50 preterm newborns, weighing less than 1500g, were enrolled. The average body mass at birth was 1086.52g ± 247.94g, with extremes at 660 and 1495g.

Analysis of clusters for population subgroups within the batch initially identifies two categories of preterm with common characters based on parameters: weight at birth, maximum weight loss, duration of the highest weight loss after birth, day the prematurity began to rise again, the day he recovered the birth weight and the day when the extrauterine growth rate became equal to the intrauterine growth rate. However, grouping is different if used as a birth weight definition parameter - 3 distinct groups are identified. Because of this dilemma, statistical analysis was preferred using the 3 groups: group 1 with an average Gn of 809 ± 82g and comprising 16 preterm and 32% of the batch; group 2 with a mean Gn of 110.59 ± 97.55g of 22 preterm, representing the majority - 44% of the batch and group 3 with a mean birth weight of 1430.4 ± 72.4g of 12 preterm, representing 24% of the lot.

The total mean protein intake, susceptible to induction, was 3 g / kg / day in all three groups (group 1 - 3.13 ± 0.24, group 2 - 3.11 ± 0.1, group 3 - 3,2 ± 0,1) and 100 kcal / kg / day for group 1 and 2 and 80kcal / kg / day for group 3. The initiation of group 1 and 2 growth occurred on average 7 days after birth, and in group 3 on the 4th postnatal day.

Parenteral nutrition was required, on average in the first 9.82 ± 1.68 days for group 1; in group 2 9.73 ± 0.46 days and in group 3, 8.35 ± 0.8 days. In none of the groups, parenteral intake was at the level of recommendations for parenteral minimal nutrition (on average 57% for gr1, 68% for group 2 and 65% for group 3, from the minimum of parental nutrition recommendations).

The enteral protein intake provides a quantity equivalent to that of parenteral intake on day 7 in group 1 and 2 and on day 5-6 in group 3.

Aportul total de proteine, ramâne subliminal recomandărilor, până în ziua a 14-a la grupul 1; la grupul 2 – între zilele 7-14, și ziua a 6-a la grupul 3.

Protein intake at Δ L = 0 (the time at which postnatal weight had equivalent markers on the Lubchenco curves as in intrauterine life) was: 4.12 ± 0.44 g / kg / day for group 1, 3.96 ± 0.12g / kg / day for group 2, and 3.8 ± 0.15g / kg / day for group 3.

Enteral intake reached the required volume for initiation of fortification, on average 10 days postnatally for groups 1 and 2, and 7 postnatal days for group 3.

Analysis of the influence of protein intake on the development of prematurity.

❖ In the first group weight gain was on average 2227g, with an average growth rate of 29.04g / day. Weight loss reached a peak on day 4-5. On average, premature babies start to rise from day 7, weight reaches birth value on day 12. Premature birth disturbs growth after 12 days. They will have the same rhythm of growth as in the intrauterine life (the same Cartesian coordinates on the fetal growth curves - denoted in the thesis with Δ L = 0), only after 7 weeks.

Data analysis suggests that an intake of 3 g / kg and 100 kcal / kg per day is likely to cause premature growth with Gn below 1000 g. The growth rate becomes identical to that in intrauterine life, 49 days after birth when are fed exclusively enterally.

Using multiple linear regressions for predictive factors, it is determined that total protein intake is correlated with weight loss, weight recovery time, growth initiation time, hospitalization duration, discharge weight, discharge weight, weight gain at discharge, where the growth rate is equivalent to that of intrauterine life and the weighting index at discharge.

- For the 2nd group, the days of hospitalization were 51.55 ± 8.1, with an average weight gain of 29.66 g / day. The moment when the rhythm of growth is similar to that of intrauterine life was at day 40. Nutrition in the first 7 days of life is strongly correlated with all the parameters that define the nutritional recovery of preterm. With the help of multiple linear regressions the author has established predictive associations using predictors of certain moments of nutrition from the first week of life. For weight loss, protein intake values on Day 1, 4 and 5 could be predictive.

The first model explains 88% of the variation in weight loss and has as a predictive factor only the total parenteral intake from the first day of life. This highlights the importance of initiating protein intake from day one. The second model explains 99.7% of the weight loss variation, and uses as a combination of predictors the total protein intake of the first day and the 5 day enteral intake (mean weight loss was 4.55 days, so in the first 4-5 days). Again, the importance of initiation of early enterobal nutrition and aggressive progression emerges. Model 3 is complete and is based on total protein intake on day 1, enteral protein intake on day 4 and enteral protein intake on day 5. Indeed, from day 1 onwards, the regression equation shows total intake not parenteral. This already obliges to initiate enterobal nutrition from the first day.

The predictive mathematical model for the resumption of growth, found as predictors: total protein intake on day 2, enteral protein intake on day 3 and 7.

Protein intake in the first week of life affects the duration of hospitalization. The predictive model is dependent on the 6th day enteral infusion, 5th day parenteral intake and 5th day total protein intake.

The weight at discharge is dependent on the protein intake from the first week of life.

- For Group 3 by approximation, we can say that in order to induce the increase of premature Gn 1200-1500 g, there are sufficient 3 g / kg and 80 kcal / kg. The duration of hospitalization was 38 ± 7.12 days. the growth rate of intrauterine life resumed on day 24. The weight gain was on average 38 g / day.

The models underline the importance of initiating early enteropathy.

Mathematical models for prediction of discharge weight indicate its dependence on protein intake in the first week of life - days 2, 3, 6 and 7, with source of parenteral and enteral nutrition.

All three preterm groups started to grow at a time when the protein intake was over 3 g / kg, the difference being that prematurity in the Gn group of 1200-1500 g became faster postnatal at this time (day 5), while groups 1 and 2 (less than 1200 g) later arrived to have this protein intake (on average 7th day). This is also due to better food tolerance in preterm with Gn over 1200g.

The 7th day of energy supply (for premature babies weighing less than 1,200g at birth) and 4th day (for the preterm with Gn 1200-1500g), the age at which the weight gain was resumed, was different.

Biological balance of preterm

Throughout the parenteral nutrition for the three groups, elevated levels of urea were recorded, with peak on days 6-7 and returning to normal after stopping parenteral protein intake.Valorile medii ale creatininei serice, deşi în creştere, nu depășesc limita maxim admisă.

In most days, mean values of proteinemia were maintained above the minimum admitted limit (4 mg / dl), but group 3 had higher values.

Complications of prematurity

One case of grade 3/4 intraventricular haemorrhage in a preterm from group 1; 8 cases of chronic pulmonary disease (group 1). 6% of preterm from group 3 did not need respiratory support. Mechanically ventilated were 27.3% of preterm with Gn below 1000 g, 18.2% of preterm with Gn 1000-1200 g, after ventilation continued respiratory support in CPAP regime. Premature anemia occurred in 100% of those under 1200g and 64.7% in over 1200g. 18% of preterm less than 1000g required 3-4 red blood cell transfusions. Retinopathy of stage 3 premature was recorded in 18% of group 1, stage 2 in 27.3% of group 2 and 23.5% in stage 3 of group 3.

3 DISCUSSION

Parenteral protein intake has been kept below the minimum limit of recommendations in nutrition guidelines. This was necessary for several reasons. First of all, we tried to minimize the side effects of parenteral nutrition. Secondly, invariably, there were reasons for restriction - increased uric and serum creatinine levels to the limit or even above the maximum limit, elevations in transaminases and alkaline phosphatase, which translate hepatic impairment. Thirdly, and the most important reason, it was attempted to save volume of fluid to create a reserve to increase enteral intake.

Early enteral breast milk intake provides a small amount of protein compared to artificial formulations or parenteral nutrition in the first 7-10 of life. For this reason, total protein intake is relatively small if we refer to recommendations.

However, the relative protein "handicap" given by this strategy from the first week brings enormous benefits in the second week of life. As it started from the first day, at week 2, the progression of maternal milk intake reaches allowances that allow the fortification and addition of protein supplement. Fortification and addition of protein supplement enrich breast milk not only with protein extracts, but also energy with oligo and micronutrients, vitamins, etc. This makes the need for parenteral nutrition to decrease dramatically and to greatly reduce the duration of parenteral intake.

Eliminating the parenteral intake as quickly as possible from the scheme is an important goal. In addition to side effects of parenteral nutrition per se (metabolic acidosis, fatty emboli, allergic reactions, hepatic impairment, PCB, cerebral haemorrhage, diselectrolytes, metabolic imbalances, etc.), the risk of sepsis (catheter infection, increased septicemia lipid nutrition).

Enteral nutrition brings in addition to parenteral nutrition, trace elements and vitamins that act as biocatalysts. Some of these are also not available in parenteral nutrition (chrome, copper, manganese, molybdenum).

Research results indicate that early enteral nutrition (day 2-3) has a protective role in the onset or duration of complications of prematurity.

4 CONCLUSIONS

1. Nutrition plays an extremely important role in premature neonatal recovery, as well as preventing or minimizing short and long-term complications.
2. Parenteral nutrition is indispensable in prematurity with Gn under 32 weeks and 1500g.
3. Proteins play a key role regardless of the type of nutrition. In the case of parenteral nutrition, protein intake is good starting from the very first hours of birth.

4. The enteral source is the key. The study highlighted the importance of nutrition with breast milk from the first day of birth. The volume of mother milk administered should be increased daily up to the limit of digestive tolerance. Our recommendation is to force digestive tolerance by increasing the number of meals (8-10 meals) with slow batch gavage.
5. There appears to be a disappointingly low protein intake to a total of liquids that tends to exceed the recommendations. The increase in the volume of breast milk should not be forgotten. The first objective to be considered is to reach a volume of 100ml / kg / day as soon as possible in order to be able to fortify. Once this goal has been achieved, it is found that the need for parenteral nutrition decreases dramatically.
6. The results of the study suggest that certain complications of prematurity may be minimal or absent when enteral nutrition is initiated early. The protective role of breast milk enterobal nutrition may be exerted by the complexity of the nutrients that are present in it - vitamins, antioxidants, growth hormones, probiotic bacteria, protein and lipid quality, an optimal ratio of nutrients, trace elements of biocatalysts. Last but not least, it is a natural way to make nutrition with an age-specific food.
7. The study also mentions that urea and creatinine tend to increase in the first postnatal week, with a return to minimal values after switching off parenteral nutrition. It is possible that kidney immaturity has a key role, but coincidence in which values normalize after stopping parenteral nutrition suggests its toxicity. Obviously, parenteral nutrition should not be suspended. Practitioners should be advised that this is unavoidable, parenteral nutrition should be duly diminished, and enteral nutrition further increased.
8. The thesis emphasizes the role of "support" of parenteral nutrition and the main objective is enteral nutrition.
9. Regardless of the type of nutrition, we expect to induce premature growth, with a protein intake of over 3g / kg / day, regardless of birth weight. It is not the only condition to trigger growth. A caloric intake of 100kcal / kg / day is an excellent catalyst to trigger growth.
10. To achieve a record recovery of premature birth, it is absolutely necessary to reduce the weight loss and duration.
11. Enteral nutrition occurs in diminishing post-weight loss, shortening the period of weight recovery from birth, but especially in recovering the fetal growth rate in a record time. The essential condition is that enteral nutrition is initiated from the first day of birth, and increased rapidly, so that on 9th-10th day diets become exclusively enteral. Although the formulas provide a higher protein intake than breast milk, they are avoided as they are not so well tolerated and will react to the rapid progression test. We administered a single formula meal at one hour to which the mother is not available for breastfeeding (3am). If it is necessary to use milk formulas, our recommendation would be to use intensely hydrolysed formulations in the first 2-3 weeks, then replace it with a preterm formula for the manufacturer's specifications.
12. Because nutrition involves sophisticated, multivariate, transformations (mEq in mg or IU, grams and calories / kg / day), as well as sophisticated interactions between parenteral nutrition principles (kcal / 1g protein ratio, amount of calories provided by glucose, protein / 100kcal), the intake of each nutritional principle (formula type, protein supplement, breast milk, colostrum, etc.), limiting conditions for the clinical status of the premature (cerebral hemorrhage, chronic pulmonary disease, renal or hepatic, etc.), biological status (increase in urea, creatinine, transaminases, metabolic acidosis with anion gap over 16, etc.), external conditions that interfere with fluid or nutrient needs (phototherapy, mechanical ventilation, etc.) with the age or weight of the prematurity - these calculations take time and predispose to errors (by omitting c CONDITIONS OF). To overcome these shortcomings, we have developed a computerized application designed to ease calculations, reduce omission errors, and create a more detailed picture of the need, progression, progress, help the practitioner better orientate with the guidelines .

13. The Excel application, we hope to be the first step in developing a computerized program available in a web format that will allow for a national registry of premature nutrition.
14. The method of study presented in the thesis, we intend to include it in this program. Thus, with the collection of data input by practitioners, they bring new statistical landmarks in real time. This would act as a dynamic benchmark for the practitioner, beyond the rigid recommendations of national guidelines. I also believe that it would allow for new standards to be introduced in premature nutrition by gathering clinical records without the need for experimental studies on such a fragile field.

ANNEX 1

SYNTHESIS OF ANALYZED PARAMETERS (average and standard deviation)

PARAMETER	THE GROUP 1 (Gn<1000g)	THE GROUP 2 (Gn 1000-1200g)	THE GROUP 3 (Gn 1200-1500g)
Gn (g)	875±105	1105±58	1371±112
Weight loss	118±44	119±15	119±14
The percentage decrease in G	13,9±5%	10,8±1,5%	8,7±1%
Length of decrease in G (days)	4,55±0,9	4,55±0,5	3,29±0,4
Initiating Growth (Day)	7±1,5	6,55±1,2	4,35±0,6
Gn Recovery (Day	11,9±2,7	12±0,77	7±1,4
Difference in discharge percentiles	19,7±19	12,7±6	3,5±7
The time at which Δ L = 0 (days)	49,55±17	39.4±12	24±9.6
Age of gestation (weeks)	26,5	29,4±0,7	29,88±0,69
Protein intake at resumption of growth (g / kg / day)	3,13±0,24	3,11±0,1	3,2±0,1
Energy input to resumption of growth (Kcal / kg / day)	102,23,7	96,2±17	76,05±8,64
Protein intake at time Δ L = 0 (g / kg / day)	4.12±0.44	3.96±0.12	3.8±0.15
Weighting index at birth	1,97±0,18	2,15±0,12	2,25±0,09
Weighted weight at discharge	2,69±0,21	2,61±0,08	2,44±0,15
Length of hospitalization (days)	76±13	51±7,9	38±7,12
Height at birth (cm)	35±1,9	37,23±0,8	39,32±0,91
Extension Sleeve (cm)	48,55±1,5	46,45±0,9	47±1
Parenteral nutrition duration (days)	9,82±1,68	9,73±0,46	8,35±0,8