

REVIEW

Impact of Early Aggressive Nutrition on Retinal Development in Premature Infants

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Summary

The normal retinal development is interrupted by preterm birth and a retinopathy of prematurity (ROP) may develop as its consequence. ROP is characterised by aberrant vessel formation in the retina as a response to multiple risk factors influencing the process of retinal angiogenesis. Insulin-like growth factor I (IGF-1) and vascular endothelial growth factor (VEGF) play an important role in the process of normal retinal vascularisation. Insufficient nutrition during the first 4 postnatal weeks results in low serum levels of IGF-1, which is essential for correct retinal vessels formation, ensuring survival of the newly formed endothelial cells. Low IGF-1 level results in stop of angiogenesis in the retina, leaving it avascular and prompting the onset of ROP. Keeping the newborns in a positive energetic balance by providing enough nutrients and energy has a beneficial impact on their growth, neurodevelopment and decreased incidence of ROP. The best way to achieve this is the early parenteral nutrition with the high content of nutrients combined with early enteral feeding by the own mother's breast milk. Multiple studies confirmed the safety and efficacy of early aggressive nutrition but information about its long-term effects on the metabolism, growth and development is still needed.

Key words

Nutrition • ROP • IGF-1 • Preterm infant

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Introduction

Retinopathy of prematurity (ROP) is a neovascular disease of the retina affecting extremely preterm infants born mostly before the 32-nd week of gestation with birth weight (BW) less than 1,500 grams (Wilkinson *et al.* 2008). Its onset is a result of interruption of normal retinal development which is caused by premature birth. The following aberrant vascularisation of retina can cause retinal scarring, detachment and subsequent blindness. With the gradual improvement in neonatal care, and thus an increase in the amount of surviving extremely premature babies, ROP remains the most prevalent cause of childhood blindness and vision impairment. It leads to approximately 15 % of all cases of visual loss in developed countries and up to 60 % in middle income countries (Gogate *et al.* 2011), where approximately one third of very low birth weight infants develop some form of ROP (Cavallaro *et al.* 2014). While the incidence of ROP in developed

countries is 5-8 %, it raises up to 30 % in medium-developed countries (Gergely and Gerinec 2010), probably due to limited financial resources. The incidence also increases with decreasing gestational age (GA) and birth weight (BW).

Multiple risk factors have been confirmed or strongly suggested for the onset of ROP. Prematurity is considered to be the main risk factor, followed by hyperoxia and unstable saturation, possible genetic predisposition, gender and race, hyperglycemia, multiple blood transfusions, administration of erythropoietin (EPO) and also nutritional status along with low BW. This multifactoriality makes its prevention and management complicated. Better understanding of the pathophysiology of ROP has allowed various preventive strategies to be devised and implemented, targeting some of the important risk factors. Currently, appropriate nutrition in preterm infants and its influence on retinal maturation is accentuated. Nutritional support as a part of postnatal care is relatively well controllable and the connection between poor nutrition, slowed postnatal growth, and the development of ROP has been established in multiple studies (Van der Veen *et al.* 2013, Stoltz Sjöström *et al.* 2016, Porcelli and Weaver 2010, Wu *et al.* 2012, Hellström *et al.* 2010). By providing an appropriate nutrition and avoiding extrauterine growth restriction in extremely preterm infants we can eliminate one of the many factors contributing to this disease.

Normal versus pathological development of retina

The development of retina starts during the fourth month and continues into the 40th week of gestation. An extremely premature infant is therefore born with incomplete retinal vasculature. Retinal blood vessels grow from the middle of the optic disk outwards to reach the ora serrata while the periphery stays avascular until approximately 32nd week of gestation. This retinal tissue is then in a state of relative hypoxia, which acts as a stimulus for hypoxia-inducible factors (HIFs) to trigger the transcription of angiogenic genes to produce growth factors, such as VEGF, its analog placental growth factor (PlGF) and the proangiogenic EPO. VEGF follows this wave of physiological tissue hypoxia and stimulates production of new endothelial cells (vasculogenesis) and subsequent budding of new blood vessels from these cells (angiogenesis) (Hartnett

2015). VEGF-mediated vascularisation is controlled by IGF-1, which is essential for the survival and proliferation of the new endothelial cells (Hård *et al.* 2013). The synthesis of IGF-I is regulated by the availability of amino acids and depends on overall energy intake. It would therefore be safe to say that IGF-1 levels reflect the state of nutrition. During the third trimester, when sufficient nutrition is available, the levels normally increase two to three times, promoting protein accretion and fast fetal growth (Fowden 2003).

This carefully organised process needs the intrauterine environment to unfold correctly. The maternal-fetal interaction in utero provides suitable oxygen levels stimulating the growth of retinal vasculature, optimal nutrition for rapid growth and development and other factors unique to the intrauterine environment. The amniotic fluid itself is not only a cushioning medium; it contains lipids, carbohydrates, enzymes, essential amino acids, which diffuse in through the placental membranes. Various growth factors are also present in levels comparable to those in maternal breast milk, including IGF-1 and EPO. The periodic ingestion of amniotic fluid promotes the development of the fetal gut and has positive influence on birth weight (Underwood *et al.* 2005, Underwood 2013).

With preterm birth, the infant suddenly loses these optimal conditions and has to cope with the harsh extrauterine environment, which it is poorly adapted for. The relative hyperoxia inhibits the expression of HIFs and VEGF, interrupting the growth of retinal blood vessels. Extremely premature newborns usually require oxygen during stabilisation or resuscitation after birth and many of them need further oxygen therapy, often lasting for days. ROP belongs to the group of neonatal free radical diseases, since the retinal tissue itself is highly susceptible to oxidative injury with its high oxygen consumption, constant exposure to light and rich content of easily oxidisable LCPUFA (long-chain polyunsaturated fatty acids), mainly DHA (docosahexaenoic acid) (Kim and Byzova 2014). Premature infants are also deficient in antioxidant defense to counterbalance this reactive oxygen species (ROS) increase (Sapieha *et al.* 2010). Oxidative stress resulting from inflammatory response during infection and sepsis or from long term parenteral nutrition also contributes to the retinal tissue injury. Fluctuations in oxygen saturation seem to be more damaging than sustained hyperoxia. It has been suggested, that it takes no more than six intermittent hypoxia episodes and subsequent

reoxygenation for the accumulation of ROS in the choroid, causing irreversible oxidative damage to the retina in newborn rats (Beharry *et al.* 2013). Aimed to minimise the oxidative injury in preterm babies receiving oxygen, the saturation targets are recommended to be between 90 and 94 % (Sweet *et al.* 2016).

After birth, as the infant loses the feto-maternal interaction, the levels of IGF-1 drop significantly. If a prolonged undernutrition follows, its increase is slow and insufficient resulting in growth restriction and higher vulnerability to ROP development. Fetal serum IGF-1 levels have been reported to correlate with birth weight, which is considered to be one of the risk factors of ROP. IGF-1 levels in small for gestational age (SGA) newborns were lower than those in eutrophic newborns (Lassarre *et al.* 1991). Interestingly, a positive correlation between intrauterine growth restriction and incidence of ROP was reported. Among the infants with ROP there was a higher number of SGA newborns compared to group without ROP – 32 % vs. 19 %, respectively (Darlow *et al.* 2005, Allegaert *et al.* 2003).

The important role of IGF-1 in the normal development of retinal vasculature and its close relation to nutritional status of the infant explain the urgent need for appropriate nutrition in preterm newborns. The adequate nutrition is reflected by postnatal weight gain and head growth. Poor weight gain, especially during the first 4 weeks of postnatal life, has been identified as a strong independent risk factor in the onset of ROP (Porcelli and Weaver 2010). Slow postnatal head growth has also been suggested to coincide with retinal vascular suppression; however more studies are needed (Löfqvist *et al.* 2006).

Development of ROP

ROP develops in two phases: The first phase is vasoobliterative, caused by interrupted and delayed angiogenesis. The levels of HIF, VEGF, IGF-1 and EPO are all decreased during this phase (Cavallaro *et al.* 2014). As the newborn grows, there is an increase in metabolic demands and the retina starts to experience hypoxia, which upregulates the synthesis of VEGF with its subsequent accumulation in the retina and the vitreous body. If the nutrition is insufficient at this stage, serum levels of IGF-1 are low and angiogenesis does not occur effectively even if VEGF is present, since without IGF-1 the endothelial cells undergo excessive apoptosis (Hellström *et al.* 2001). When the serum IGF-1 catches

up and rises to its threshold level, it prompts a transition into the second, vasoproliferative phase of ROP at around 32-34 weeks of postconceptional age. Rapid pathological neoangiogenesis is triggered manifesting at first as a faint demarcation line between the vascular and avascular retina – stage 1 according to International Committee For The Classification of Retinopathy of Prematurity (2005), then raising this junction into a ridge – stage 2. These first two stages can regress spontaneously and are considered as early or mild ROP. The pathological vasculature can continue growing outside the retinal plane – stage 3, the vascular stage. These new blood vessels are subpar and fragile and can bleed into the vitreous body which causes fibrotisation, traction and finally retinal detachment resulting in blindness – stages 4 and 5, the fibrovascular stage.

Aggressive early nutrition and its impact on retinal development

A sufficient caloric intake and adequate amount of nutrients can prevent the postnatal gap in weight gain and IGF-1 levels and thus promote the catch-up growth and development in preterm infants. The current guidelines emphasise the importance of optimal nutrition similar to that in utero by starting the aggressive balanced parenteral nutrition and initiating enteral feeding as soon as possible, preferably on the first day of life.

Caloric requirements

The estimated daily energy accretion in utero is approximately 24 kcal/kg/day during the 24-28 weeks of gestation, rising slightly up to approximately 38 kcal/kg/day for the remaining period of gestation (Denne 2001). Metabolic demands of very preterm newborns are high; their energy reserves are limited and quickly depleted. An infant aged 24 gestational weeks weighing 500 g has only <1 % of body fat and 90 % of the body consists of water. There is an estimate that the energy supply in an infant weighing 1,000 g serves only for 4-5 days (Embleton 2007). Due to the large relative surface area heat loss happens at a faster rate; therefore more energy is expended for thermogenesis. Perinatal infection, lung disease and other pathologies often affecting extremely low birth weight infants (ELBWI) result in even higher consumption of energy. In a premature infant the total energy expenditure can exceed 60 kcal/kg/day, rising up to 85 kcal/kg/day in ELBWI (Koletzko *et al.* 2005). The energy requirement

in ELBWI increases along with the postconceptional age and it is up to 111 kcal/kg/day (89+/-22 kcal/kg/day) in the 34-38th week, which is in about 55 % higher than in term infants (Guilfooy *et al.* 2008). The minimal energy intake should not be lower than 110 kcal/g/day to meet all the energetic demands but even higher intake (up to 120 kcal/kg/day) may be needed to facilitate maximum protein accretion for optimal growth (Koletzko *et al.* 2005). Based on current data, 110-135 kcal/g/day is the most appropriate range of energy requirements in a growing premature newborn on full enteral feeding (Hulzebos and Sauer 2007, Agostoni *et al.* 2010). In case of total parenteral nutrition, the recommendations are lower, about 90-100 kcal/kg/day, since no energy is expended for digestion and none is lost in stools (Koletzko *et al.* 2005). Low energy supply during the first 4 weeks after birth has been identified in a recent study as an independent risk factor for ROP also suggesting that the minimum recommended parenteral caloric intake lower than 110 kcal/kg/day might be insufficient. According to their findings, the increase in caloric intake by 10 kcal/kg/day during the first month can decrease the risk of severe ROP by 24 % (Stoltz Sjöström *et al.* 2016).

Amino acids

The sufficient intake of amino acids (AA) is essential for protein synthesis and growth. The minimum daily intake of AA to prevent catabolism is about 1.5 g/kg (Embleton 2007). Positive nitrogen balance and adequate protein accretion for optimal growth is achieved by administration of 2.0-3.5 g/kg/day of AA from the first day. The amount of AA should be increased to the target of 4.0-4.5 g/kg/day (Agostoni *et al.* 2010, Patel and Bhatia 2017) together with sufficient caloric intake to cover their metabolism.

In the past AA were administered with great caution, mostly out of concern that early AA intake may cause hyperammonemia, excessive uremia and metabolic acidosis. The explanation for these adverse effects may be probably the composition of the first AA solutions (te Braake *et al.* 2005). It has been shown, that blood urea nitrogen (BUN) levels do not correlate with early parenteral protein intake in VLBW infants and have the tendency to steady decrease despite the high AA intake (Ridout *et al.* 2004, Roggero *et al.* 2010). Restriction of AA intake below 4.0 g/kg/day did not have any significance in prevention of BUN increase (Weintraub *et al.* 2015). Metabolic acidosis seems to develop in ELBW

infants during the first days of life regardless the dosage and duration of AA administration (Jadhav *et al.* 2007).

In current practice the early administration of AA is recommended, it can be well tolerated immediately after birth and has been shown to promote weight gain, protein accretion, anabolism and positive nitrogen balance. Several comparative studies did not reveal any adverse effects of AA on the metabolism and it is deemed that the early high intake of AA is safe for preterm infants (Valentine *et al.* 2009, Lee *et al.* 2013, Hay and Thureen 2010).

Despite of these benefits there are also reports concerning the risks of early high intake of AA. One possible adverse effect that has been noted in recent studies is the influence of high AA doses on the metabolism of phosphorus and calcium. Hypophosphatemia and hypercalcemia were detected and attributed to a form of refeeding syndrome triggered by high AA intake, without sufficient supplementation of other micronutrients (Mizumoto *et al.* 2012, Ichikawa *et al.* 2012, Nesargi *et al.* 2012). Refeeding syndrome is defined as a metabolic syndrome induced by a rapid anabolism caused by increased insulin secretion after sudden nutrient intake following previous starvation or malnutrition. The results are hypophosphatemia, hypokalemia, hypomagnesemia, arrhythmia, edema and congestive heart failure. Its incidence in children is not well known, however the hypophosphatemia in preterm newborns seems to happen on a similar basis. During the anabolic stage, in a growing infant, the phosphorus uptake by the cells is increased. After depletion of phosphorus in plasma it is released from bones along with calcium, causing subsequent hypercalcemia as well (Bonsante *et al.* 2013).

Even though there is increasing evidence of the short-term benefits of early aggressive AA administration, the data concerning the long-term outcomes is still missing.

Glucose

Glucose is a major source of energy for immature brain. It serves also as a substrate for the synthesis of fatty acids and nonessential amino acids and the energy released by 1 gram is 4 kcal. Preterm infants have higher endogenous glucose production than healthy term infants; it can reach up to 8.3 mg/kg/min (Koletzko *et al.* 2005). To match to this increased endogenous production, an adequate intake of intravenous glucose is 6-8 mg/kg/min started shortly after birth (Hay 2008).

Careful monitoring of glycemic status is essential, since even the recommended infusion rate might cause hyperglycemia (Hay 2013). Higher serum glucose concentration has other adverse effects, such as increased serum osmolarity, osmotic diuresis and increased fat deposition resulting in liver steatosis, since the excess glucose is stored as fat. The added metabolic processes further increase energy expenditure (Fusch *et al.* 2009).

Hyperglycemia is a common complication in extremely preterm infants and it may develop in more than 50-80 % out of ELBWI due to various reasons: excessive glucose intake, as a response to stress, thermal instability, sepsis, severe illness, corticosteroid therapy, and others (Hays *et al.* 2006, van der Lugt *et al.* 2010). Hyperglycemia is regarded as a significant risk factor of neonatal morbidity and mortality, increasing the risk of early death, sepsis, severe intraventricular hemorrhage and also ROP (Hays *et al.* 2006, Kao *et al.* 2006).

The exact mechanisms of hyperglycemia induced retinal injury have not been fully identified yet. The research in diabetic retinopathy has shown that elevated glucose levels promote the oxidative stress by increased production of superoxide anion and hydrogen peroxide in the retinal cells (Ellis *et al.* 2000, Du *et al.* 2003). Additionally, the high blood glucose concentration seems to further upregulate VEGF production in retinal Müller cells during hypoxic conditions, promoting the proliferative phase of ROP (Brooks *et al.* 1998). The VEGF upregulation is even more significant if a period of hyperglycemia is followed by a sudden drop in glucose levels (Sone *et al.* 1996), as might happen in case of intravenous insulin therapy.

Many studies have focussed on the correlation between hyperglycemia and ROP suggesting persistent hyperglycemia to be an independent risk factor for the onset of the disease (Mohamed *et al.* 2013, Mohsen *et al.* 2014, Ahmadpour-Kacho *et al.* 2014, Chavez-Valdez *et al.* 2011). However the recent meta-analysis has concluded that a direct causality between hyperglycemia alone and ROP cannot be ascertained and that more studies are needed (Au *et al.* 2015). Despite of this, an interesting association between severe ROP and insulin therapy has been reported (Kaempf *et al.* 2011, Lee *et al.* 2016). Since the insulin therapy aggravates diabetic retinopathy and upregulates VEGF in the retina (Poulaki *et al.* 2002), it would be useful to pay attention also on the connection between hyperglycemia, use of insulin and ROP.

Lipids

Lipids form up to 25-40 % of non-protein daily caloric intake (Koletzko *et al.* 2005). Providing 9 kcal per gram, they are a valuable source of energy and important source of essential fatty acids as well. The sufficient lipid intake is especially important in very preterm infants, since essential fatty acid accretion in the fetus does not occur until the third trimester and then continues up to 18 months postnatally. A preterm infant weighing less than 1,000 g only contains 1 % of fat and will lose 1.2 g/day of that storage, if not supplemented with lipids (Salama *et al.* 2015). During the last months of gestation there is a significant placental transfer of LCPUFAs, which are essential for the correct development of the central nervous system and the retina. The omega-6 arachidonic acid (ARA), the omega-3 DHA and its precursor eicosapentaenoic acid (EPA) are of the most physiological importance. They are the ubiquitous components of phospholipid membranes and DHA and ARA are the main fatty acids of neural and vascular retinal tissue. DHA comprises about 60 % of all retinal LCPUFAs and compared to other body tissues, retina contains the highest amount of DHA (Harris and Baack 2015, Marszalek and Lodish 2005, SanGiovanni and Mehta 2009). Omega-3 LCPUFAs protect the retinal tissue by providing anti-inflammatory, immunomodulatory and neuroprotective effects through their conversion to eicosanoids. They serve as building blocks, local signaling molecules and are able to regulate gene transcription. EPA down-regulates the VEGF receptor expression, contributing to retinal vascular stability and together with DHA reduces endothelial proliferation and migration *via* suppressing VEGF in both normoxic and hypoxic conditions (SanGiovanni and Chew 2005, Zhuang *et al.* 2013).

In humans there is a lack of enzymes for *de novo* synthesis of omega-3 and omega-6 LCPUFAs and therefore they have to be received by the diet. The foetus and later the newborn is fully dependent on the mother and gets LCPUFAs by the placental transport and then from the mother's breast milk. A premature birth prevents the infant from adequate lipid stores and along with insufficient conversion from fatty acids precursors it results in essential fatty acids deficiency in preterm newborns. Especially those infants born under the 28 week of gestation are at increased risk and the fatty acids deficiency develops within 72 h unless they are supplemented in the nutrition (Harris and Baack 2015). Commercially available intravenous lipid emulsions are

either soybean oil based, which contain medium length chain fatty acids and omega-6 LCPUFAs, but are low in omega-3 LCPUFAs, or combined with fish oil, olive oil, or coconut oil, which increases the omega-3 LCPUFAs content. There is an increasing evidence, that using the latter might provide an extra step in the prevention of ROP and improvement of neurodevelopment. The connection between omega-3 LCPUFAs, mainly DHA, and decreased risk of ROP has been reported in very recent studies. The infants receiving fish oil based lipid emulsions had lower incidence of ROP and increased DHA serum levels (Beken *et al.* 2014, Pawlik *et al.* 2014, Fu *et al.* 2015). The early high intake of intravenous lipids has been associated with lower incidence of ROP even though the used lipid emulsion was low in omega-3 LCPUFAs (Van der Veen *et al.* 2013). There is the evidence that lipid preparations containing more omega-3 LCPUFAs may be more beneficial to the nutritional status, improving the fatty acid profile, while being safe and well tolerated (Rayyan *et al.* 2012, Dai *et al.* 2016).

Based on ESPGHAN guidelines, lipid supplementation is recommended in preterm infants by continuous infusion at the rate of maximum 3 g/kg/day, starting with 1-2 g/kg/day on the first day with an incremental increase in lipid infusion by 0.5-1 g/kg/day until reaching the maximum dose (Koletzko *et al.* 2005). Ibrahim *et al.* (2004) have demonstrated in their study comparing early aggressive nutrition in premature newborns with the conservative model, that lipids in the dose of 3 g/kg/day started as soon as 1 h after birth were well tolerated. A recent review has evaluated the possible adverse effects of intravenous lipids administration – such as hyperbilirubinemia and kernicterus, chronic lung disease aggravation, adverse effects on the immune system and many others. The authors conclude that these past concerns about lipid intake have been disproved and the benefits of early lipid intake far outweigh the possible risks (Salama *et al.* 2015). Another study was focused on parenteral nutrition associated cholestasis (PNAC) following early lipid and protein intake. It was found, that the current trend of aggressive early nutrition poses no significant risk of PNAC but improves the weight gain, head and longitudinal growths. The incidence of PNAC was reduced significantly due to combining the aggressive parenteral nutrition with the early enteral feeding to stimulate the bile flow (Repa *et al.* 2016). In summary, early parenteral lipid infusions seem to have no

significant adverse effects and appear to be safe and well tolerated (Vlaardingerbroek *et al.* 2012).

Enteral feeding

The importance of early enteral feeding or “priming” has been well established. While parenteral nutrition is essential to deliver sufficient caloric intake to the very preterm infant during the first days after birth, enteral feeding is vital to further development of the digestive tract. At around 25 weeks of gestation the fetal gut is already structurally very similar to adult one. With the villous architecture established and digestive enzymes mostly functional, the gut has enough capacity to digest and tolerate enteral feeds (Newell 1996). The enteral nutrition should start as soon as possible; from the first day if the baby is hemodynamically stable (Sweet *et al.* 2016).

The mother’s own breast milk is the best choice for any infant, immunologically and nutritionally tailored to meet the needs of a baby from the very beginning. Colostrum has an important immunologic and trophic significance, being rich in IgA, lactoferrin, while lower in nutritive components, such as minerals and lactose (Ballard and Morrow 2013). The colostrum of mothers who delivered preterm is even richer in these immunomodulatory components, albeit with high variability (Castellote *et al.* 2011). The early colostrum contains also high amounts of IGF-1, IGF-2 and IGF binding proteins. During the first three days of lactation the IGF-1 level is higher in about 80 % when compared to its content in mature breast milk (Eriksson *et al.* 1993). In addition to IGF, colostrum has a high concentration of vitamin E, which decreases along with the continuation of lactation (Lima *et al.* 2014). There is also evidence that the abnormal vascularization of the retina, incidence of ROP and retinal detachment are significantly lower in very preterm infants fed by human breast milk (Manzoni *et al.* 2013, Ginovart *et al.* 2016, Okamoto *et al.* 2007, Maayan-Metzger *et al.* 2012). A very recent meta-analysis has concluded that human milk feeding promotes the physiological development of immature retina and acts as a protective factor for any stage of ROP (Zhou and Chen 2015).

Breastfeeding in preterm newborns faces many challenges and lactation in mothers may often be insufficient. Preterm formulas and banked human milk are used as substitutes, while the discussion on which one is the better choice continues. In 2014 the Cochrane meta-analysis evaluated several controlled trials

comparing the nutritional and developmental outcomes of formula fed infants versus donor milk fed infants, but the results were inconclusive. The formula fed infants displayed greater linear weight gain and head growth than the donor milk fed group, but there were no significant differences in post-discharge weight and development. Most of the studies showed an increased incidence of necrotising enterocolitis in formula fed infants along with feeding intolerance (Quigley and McGuire 2014, Boyd *et al.* 2007). However the authors emphasise the need for new studies to compare the effects and long term outcomes of different enteral feeding practices since the vast majority of these reports are over 20 years old, with inconsistent methodology and small sample size. Another thing that should be considered is the different composition of modern preterm formulas. There is also a lack of reliable data on comparing the effects of formula feeds and fortified donor milk.

Banked milk needs to be processed to eliminate potential pathogens and pasteurisation greatly influences its composition. The standard protocol is the Holder pasteurisation at 62.5 °C for 30 min. Its effects on various nutrients and bioactive components of milk differ. Certain components are significantly affected by pasteurization, such as interferon- γ , tumor necrosis factor- α , interleukin-1 β and interleukin-10 (Ewaschuk *et al.* 2011). The levels of IgA, lactoferrin and lysozyme are significantly decreased suggesting lowered efficacy of antimicrobial properties in processed donor milk (Czank *et al.* 2009, Tully *et al.* 2001). The content of LCPUFAs in pasteurized milk is not affected by Holder pasteurization and the overall content of triglycerides is only slightly decreased, however milk lipases are completely destroyed by the treatment (Tully *et al.* 2001, Henderson *et al.* 1998). Glycosaminoglycans and oligosaccharides seem to be stable. Vitamins react differently to pasteurization, while fat soluble vitamins display sufficient retention; vitamin C concentrations are consistently reduced. Even though the nutritional value of donor milk seems to be preserved, some immunoactive properties and enzymatic activity are lost by the heat treatment (Peila *et al.* 2016). Moreover, banked human milk is usually donated by mothers of healthy term infants, who have already been lactating for a longer period of time. Just like there is a compositional difference between early milk and mature milk, foremilk and hind milk, the milk of mothers who delivered preterm and the mothers of term infants also differs. Preterm milk has higher initial content of protein, fat, amino acids, calcium and sodium (Underwood 2013, Narang *et al.*

2006). Donor milk is low in DHA and amino acids (Valentine *et al.* 2010). This suggests that donor breast milk as a substitute for mother's own milk does not hold a significant advantage over the preterm formula, and that formula might better succeed in a consistent delivery of the required nutrients, without the added need for treatment.

The trials taking ROP into consideration have not found any significant difference in the incidence of ROP in both groups (14 % in formula fed infants vs. 19 % in donor milk fed infants), suggesting no benefits of donor milk feeding in terms of prevention of ROP (Schanler *et al.* 2005, Cristofalo *et al.* 2013). Increased content of essential fatty acids in infant formula may mitigate the DHA insufficiency in preterm infants. A daily enteral DHA supplementation from the first week of life on seems to increase circulating DHA levels that may have a positive impact on the neurodevelopment without any adverse effects (Baack *et al.* 2016).

Conclusions

During the second half of pregnancy the fetus accumulates large amounts of nutrients to ensure intensive growth and normal development. After preterm birth the newborn has to cope with new environment and conditions. Due to high energy consumption and low caloric reserves, extremely preterm newborns are greatly predisposed to nutritional deficiency. There is overwhelming evidence that poor status of nutrition in these patients, mainly during the first 4 weeks of postnatal life, influences negatively their outcome including development of retina. The current strategy to provide optimal nutrition in preterm newborns is aimed to mimic the intrauterine nutrient intake corresponding to the gestational age. In the past, early aggressive nutrition was not used in premature infants because of concerns over its safety. Multiple studies have been conducted and confirmed the efficiency and tolerability of this type of nutritive support. Initiation of parenteral nutrition with high contents of amino acids, lipids and glucose shortly after birth and its combination with early enteral feeding with preferably mother's own colostrum as soon as possible, is the current standard of practice. Optimised nutrition enables to maintain sufficient IGF-1 levels necessary for the correct development of retinal vasculature, for better protein accretion, weight gain, head growth and longitudinal growth as well. Maternal breast milk is the preferred feed for its high content of antioxidants and IGF-1. If unavailable, a preterm formula

seems to be the next best choice compared to banked donor milk. Despite the benefits of early aggressive nutrition strategy, more studies assessing its long term effects on further development and metabolism are needed. However, the early aggressive nutrition serves as a relatively well achievable way to lower the burden of prematurity and its consequences on the newborn's health in the future.

Conflict of Interest

There is no conflict of interest.

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