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EDITORIAL

Editorial on 'Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity' Kaempf JW *et al*.

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Severe retinopathy of prematurity (ROP) is a multifactorial disease characterized by a first phase of impaired growth and obliteration of retinal vessels leading to insufficient vascularization. The second phase of ROP with subsequent pathologic neovascularization may lead to retinal detachment and blindness. While degree of prematurity is decisive, oxygen treatment is the most studied risk factor, which, when poorly controlled, still causes blindness in relatively mature preterm babies.[1] Recently, poor weight gain during the first weeks of life has been found to be strongly associated with later ROP development,[2–4] indicating that factors causing impaired general growth also have a negative impact on retinal vessel development.

ROP is a sight-threatening condition of the most immature preterm infants and shares important features with diabetic retinopathy, which is a major cause of visual disability and blindness in adults. Both disorders are characterized by vascular endothelial growth factor (VEGF)-mediated uncontrolled retinal neovascularization under hypoxic conditions. During the last decade, hyperglycemia, the hallmark of diabetes, in the postnatal period of preterm infants has been recognized as a risk factor for ROP as well.[5–7]

In this issue of the *Journal of Perinatology*, Kaempf *et al*.[8] report the results of a retrospective study of 372 infants born before 30 weeks of gestation, confirming the association between poor weight gain and hyperglycemia during the first postnatal month and later development of ROP. Interestingly, they also report that treatment with insulin is a stronger risk factor than the hyperglycemia *per se*. As proposed by the authors, proper management guidelines in the first weeks of life, promoting growth while maintaining euglycemia, may be means to reduce ROP.

Poor weight gain is a common problem in very preterm infants, while the genesis is largely unknown. Attempts to reduce ROP by promoting growth through increased nutrition have been only partly successful.[9] It is difficult to maintain the recommended dietary intake,[10] and the most immature infants appear to lack the capability to utilize the provided nutrients, partly because of morbidities and medications (for example, steroids). In the study by Kaempf *et al*., more aggressive nutrition was associated with more hyperglycemia and insulin use, and with a tendency to develop more proliferative ROP.

The hyperglycemia of very preterm neonates has been attributed to both relative insulin resistance and defective islet β-cell processing of proinsulin.[11] Insulin-like growth factor I (IGF-I), which is essential for growth in the fetus and neonate, is known to be reduced after very preterm birth and low serum concentrations are associated with ROP.[12] IGF-I is known to counteract insulin resistance[13] and it is likely that lack of IGF-I, which possibly can be supplemented, is one factor behind preterm hyperglycemia. The effect of other factors influencing growth in the neonatal period and hence ROP need to be examined further.

The very properly designed study by Kaempf *et al*. highlights the importance of managing conditions during the first weeks of life to prevent development of proliferative ROP, which develops weeks to months later. It inspires to conduct further research to reveal neonatal factors that may be subjected to interventions in order to prevent ROP. If prevention of neonatal growth restriction can be accomplished, it is plausible that normal development of vascular and neuronal tissues will be promoted (first phase of ROP) and ROP and other morbidities of preterm birth could be prevented. In contrast, much of ROP research today focuses on treatment regimes that block growth factors such as VEGF, aiming at causing established neovascularization to regress (second phase of ROP). Intraocular injections of these extrinsic factors around term has unknown systemic effects in this population of children with already persistent subnormal growth, and impaired development and function of the central nervous system and other tissues. Preventive measures are urgent and the article by Kaempf *et al*. shows the direction to start focusing on during the first weeks of life.

Conflict of interest

Dr Ann Hellström has received compensation as scientific consultant to Premacure AB, and AH and A-LH hold shares in a company controlling Premacure AB.

A Hellström and A-L Hård
Department of Ophthalmology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
E-mail: ann.hellstrom@medfak.gu.se

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