CLINICAL STUDY

Ocular fundus abnormalities in children born before 29 weeks of gestation: a population-based study

ANN HELLSTRÖM, ANNA-LENA HÅRD, ELISABETH SVENSSON, AIMON NIKLASSON

Abstract

Purpose **Preterm birth has been found to be associated with increased morbidity of the central nervous and vascular tissues. To investigate the influence of preterm birth on the optic disc and retinal vessels, we examined the ocular fundus in school-aged children born very preterm.**

Methods **A prospective, population-based study was performed in 50 very preterm children (median age 7 years, range 5–9 years) with a median gestational age at birth of 27 weeks (range 24–28 weeks) and a median birth weight of 1055 g (range 450–1520 g). The ocular fundus was examined by ophthalmoscopy in 50 children, and the optic nerve and retinal vessel morphology was evaluated by digital image analysis of ocular fundus photographs in 45 of these children.**

Results **The median optic disc area was significantly smaller ($p = 0.0002$) in the preterm children compared with a reference group. There was no difference in cup area and, consequently, the rim area was significantly smaller ($p = 0.0002$) in the preterm children. Children with early signs of brain lesions commonly had a rim area below the median of the reference group. Preterm children also commonly had an abnormal retinal vascular pattern that was independent of a previous history of retinopathy of prematurity.**

Conclusion **Very preterm birth was associated with subnormal optic disc and rim areas and an abnormal vascular pattern. The findings clearly demonstrate the effect of preterm birth on the development of these structures. The long term clinical prognosis of these findings has yet to be determined.**

Key words Digital image analysis, Optic nerve morphology, Preterm birth, Retinal vessels, Rim area

A. Hellström
A.-L. Hård
Department of Clinical Neuroscience
Section of Ophthalmology
The Queen Silvia Children's Hospital
Göteborg, Sweden

A. Niklasson
International Pediatric Growth Research Center
Department of Pediatrics
The Queen Silvia Children's Hospital
Göteborg, Sweden

E. Svensson
Biostatistics Branch
Department of Mathematical Statistics
Chalmers University of Technology
Göteborg, Sweden

Ann Hellström, MD, PhD ✉
Section of Pediatric Ophthalmology
The Queen Silvia Children's Hospital
Sahlgrenska University Hospital/Östra
S-416 85 Göteborg, Sweden
Tel: +46 31 3435774
Fax: +46 31 3435771
e-mail: ann.hellstrom@medfak.gu.se

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Preterm birth carries a greatly increased risk of perinatal disease of the central nervous and vascular systems; for example, periventricular leucomalacia (PVL)[1] and retinopathy of prematurity (ROP).[2]

During follow-up of children previously screened for ROP, we gained the impression that they often had small and abnormally shaped optic discs. Optic disc hypoplasia has previously been defined as a reduced number of axons caused by an insult to the nerve at any time before it is fully developed.[3] In children born at a gestational age (GA) of less than 29 weeks the development of the optic nerve is far from complete, as only 75% of the growth is achieved even after 40 weeks of gestation.[4] It was suggested that preterm birth may be associated with an increased risk of optic nerve hypoplasia. Damage to the optic nerve in children born prematurely might occur prenatally and be caused by factors responsible for the preterm birth, or it may occur peri- or postnatally by morbidity associated with immaturity. During the last decades there have been few studies performed on preterm children regarding ocular and fundus appearance. These have described single cases of optic disc anomalies, such as hypoplasia, colobomatous discs, drusen and optic disc atrophy.[5–8] One morphometric study performed on fundus photographs from a selected group of preterm children with a gestational age of less than 37 weeks demonstrated no optic disc changes but an abnormal vascular pattern in the group as a whole.[9] In addition, a morphometric study performed on fundus photographs from a group of preterm children with PVL demonstrated large cups in normal-sized optic discs, which it was suggested was a variant of optic nerve hypoplasia.[10]

To our knowledge, no population-based morphometric study has been performed on the ocular fundus of very preterm children, i.e. children with a GA less than 29 weeks. Such children are of particular interest as they represent the most immature children at birth and have demonstrated a high frequency of visual dysfunction.[11,12] The present study therefore set out to determine the influence of very preterm birth on the optic disc and retinal vessels, using digital image analysis of fundus photographs.

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Materials and methods

Children born preterm

All children born at a GA of less than 29 weeks between 1988 and 1992, to mothers resident in the city of Göteborg, were enrolled in the study (n = 56). Two children could not be traced for follow-up and 3 did not turn up for their appointments, despite previous agreement from their mothers. One child was blind due to retinal detachment and could therefore not have a proper evaluation of the ocular fundus structures. Thus, 50 children, aged between 5.1 and 9.3 years, with a median GA at birth of 27 weeks (range 24–28 weeks) and a median birth weight of 1055 g (range 450–1520 g), were available for the study. All children had an eye examination, including ocular fundus photography. Only correctly focused photographs with the optic disc centred were accepted for analysis; 45 of the children (17 girls, 28 boys) fulfilled these criteria. The remaining 5 children were investigated by ophthalmoscopy. Ten children were part of a previously reported study of ocular fundus morphology in preterm children.[9] Visual acuity among the 50 children ranged from 20/100 to 20/20 (median 20/20). Refraction ranged from −10.5 to +6.25 dioptres.

Reference group

One hundred healthy individuals (56 boys, 44 girls) born at term, with an age range of 2.6–19.6 years, constituted a reference group for evaluation of ocular fundus morphology. Detailed data for these children and adolescents are presented elsewhere.[13]

The study was approved by the Committee for Ethics at the Medical Faculty, Göteborg University. Informed consent was obtained from the parents after the nature of the procedures had been fully explained.

Ophthalmological examination

All children had an ophthalmological examination, including visual acuity, visual fields, refraction and motility. A non-motor test of visual perception was also performed. Detailed data from these investigations are presented elsewhere.[14]

Ophthalmoscopy

The ocular fundus was examined by ophthalmoscopy in all children (n = 50); the optic nerve, retinal vessels and macular area were thoroughly inspected.

Digital image analysis of fundus photographs

The ocular fundus photographs were taken after cycloplegia and analysed quantitatively, using a specially designed computer-assisted digital mapping system.[15]

The optic disc area was measured by marking the outlines with a cursor. The inner border surrounding the nerve tissue defined the optic disc; care was taken not to include the white peripapillary scleral ring. The cup was defined by contour, and its definition was facilitated by the course of the vessels and its pallor. The neuroretinal rim area was obtained by subtraction of the cup area from the disc area. The indices of tortuosity for arteries and veins were defined as the path length of the vessel divided by the linear distance from the vessel origin to a reference circle 3 mm from the centre of the optic disc. Vessels were also marked from their branching point to the reference circle, and the total number of branching points (arteries and veins), i.e. retinal vessels, within this area was calculated. Only eyes with refraction values between −4 and +4 were included in the analysis in order to minimise refraction errors. Two children and 2 eyes from 2 additional children were excluded due to refraction values outside −4 and +4. The same digital analysis method was used for both the preterm children and the reference group, and all measurements were performed by the same person (A.H.).

Table 1. *Perinatal morbidity variables in 50 very preterm children*

Morbidity variables	n	Median	Range
Retinopathy of prematurity (ROP) (stage)	25	2	(1–4)
Oxygen treatment (days)	42	43	(1–447)
Assisted ventilation (days)	18	19	(1–150)
Oxygen treatment > 40% (days)	29	7	(1–361)
Blood transfusions (number)	35	6	(1–45)
C-reactive protein > 50 mg/l	7	–	–
Blood glucose < 1.7 mmol/l	13	–	–
Bronchopulmonary dysplasia	2	–	–
Positive blood culture	12	–	–
Cryo-treated for ROP	6	–	–

Retrospective file-review

Pre- and perinatal medical history

The maternity files of the mothers of the preterm children were available in all cases; there were 10 cases of gynecological bleeding, 3 cases of suspected infection at the time of delivery and 3 cases of systemic disease (diabetes, lymphoma and rheumatoid arthritis). There was no evidence, from the files, of maternal alcohol abuse during pregnancy. The time of the mother's last menstrual period was recorded, and GA was estimated by fetal ultrasonography, performed at week 17 of gestation (post-menstruation). The fetal ultrasonographic data were used to determine the GA at birth. The perinatal morbidity of the preterm children is summarised in Table 1. Perinatal data were reviewed with regard to the occurrence and treatment of ROP (stage 1–5),[2] occurrence of intracranial haemorrhage (grade I to IV),[16] duration of oxygen treatment and of assisted ventilation, duration of oxygen treament over 40%, elevated C-reactive protein (> 50 mg/l), decreased blood glucose (< 1.7 mmol/l), number of blood transfusions and occurrence of positive blood culture during hospitalisation. Hospital and Child Health Care Unit files were also reviewed with regard to health status and neurological development before the time of the eye examination.

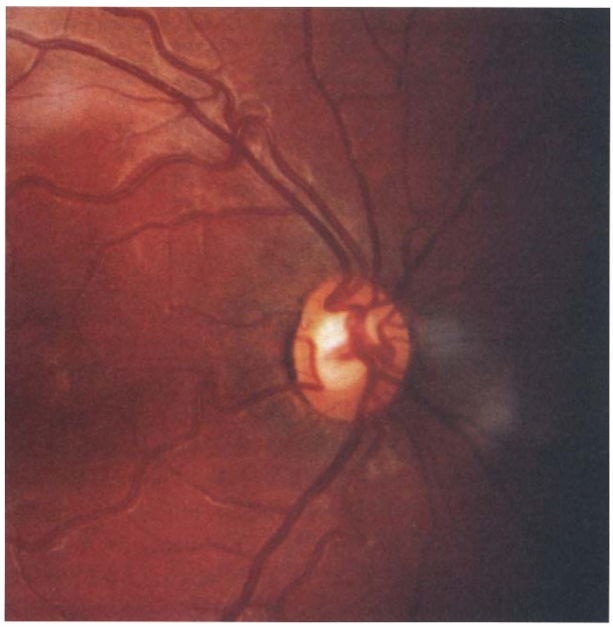

Fig. 1. *Fundus photograph of a 6-year-old boy born at 28 weeks of gestation, whose results were below the 2nd percentile on the visual perceptual test, demonstrating a relatively large cup in a small optic disc and abnormal vascular pattern with tortuous retinal arteries.*

Postnatal medical history

Five children had cerebral paresis (four spastic diplegia and one right hemiparesis). Two of these 5 children had undergone neuro-imaging that had verified PVL. An additional child without cerebral paresis had PVL verified by magnetic resonance imaging (MRI).

A review of the hospital files of the preterm children for the period from hospital discharge until their eye examination revealed that most of the children had suffered only from minor illnesses, such as infections.

Statistical methods

The ocular fundus variables for each child were calculated from the mean of the two eye measurements. The median and 95% confidence interval (CI) for the median were calculated for optic disc, cup, rim areas and for tortuosity for arteries and veins as well as for number of vascular branching points. The Wilcoxon Mann–Whitney test was used to compare the medians of the group of preterm children with the reference group.

Table 2. *Ocular fundus abnormalities, as analysed by digital image analysis, in 45 very preterm children*

Ocular fundus variable	No. of preterm children
Small optic disc area[a]	9 (20%)
Zero optic cup area	9 (20%)
Large cup in normal-sized optic disc	1 (2%)
Small neuroretinal rim area[a]	8 (18%)
Tortuous retinal arteries[b]	35 (78%)
Tortuous retinal veins[b]	1 (2%)
Reduced number of vascular branching points[a]	8 (17%)

[a]Below the 5th centile of the reference group of healthy full-term children.[13]
[b]Above the 95th centile of the reference group of healthy full-term children.[13]

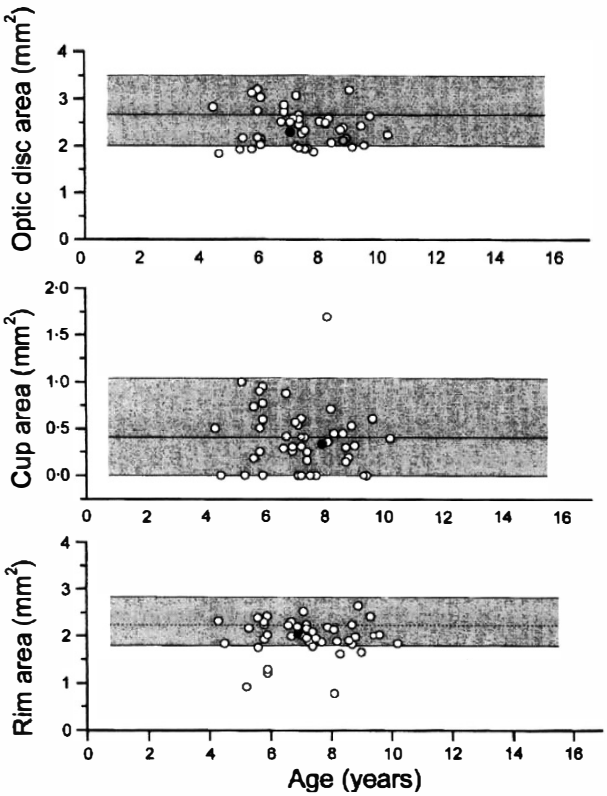

Fig. 2. *Optic disc, cup and rim areas in 45 children born very preterm. The shaded area depicts the 5th to the 95th centile range for the healthy reference group (optic disc 2.01–3.50 mm², optic cup 0–1.04 mm² and optic rim 1.79–2.83 mm²) and the centreline indicates the median for the health reference group.[13] The median for the preterm group is marked with a filled circle.*

Results

Optic nerve morphology

Children born preterm had significantly different ocular fundus morphology compared with the reference group of full-term children (Fig. 1). This was exemplified by a smaller optic disc area compared with the reference group of healthy children (median 2.35 and 2.67 mm², respectively; $p = 0.0002$; Fig. 2, Table 2). The 95% CI for the median of the optic disc area among the preterm children was 2.17–2.50 mm². In addition, the preterm children had a significantly smaller rim area than the reference group (median 2.03 and 2.24 mm², respectively; $p = 0.0002$). The 95% CI for the median of the rim area among the preterm children was 1.95–2.14 mm². No difference was found in the median cup area between the two groups (0.36 vs 0.41 mm²; $p = 0.57$). A cup was noted in 36 of the 45 (80%) preterm children and in 88% of the reference group.

Optic nerve morphology was independent of the perinatal morbidity listed in Table 1.

Optic nerve morphology and clinical symptoms

Eleven children had a visual acuity ≤ 0.8. Ten of these children were investigated by digital image analysis and all had a rim area below the median of the reference group. In addition 7 of these 10 children analysed had scores below the 2nd percentile as assessed by a visual perceptual test.[14]

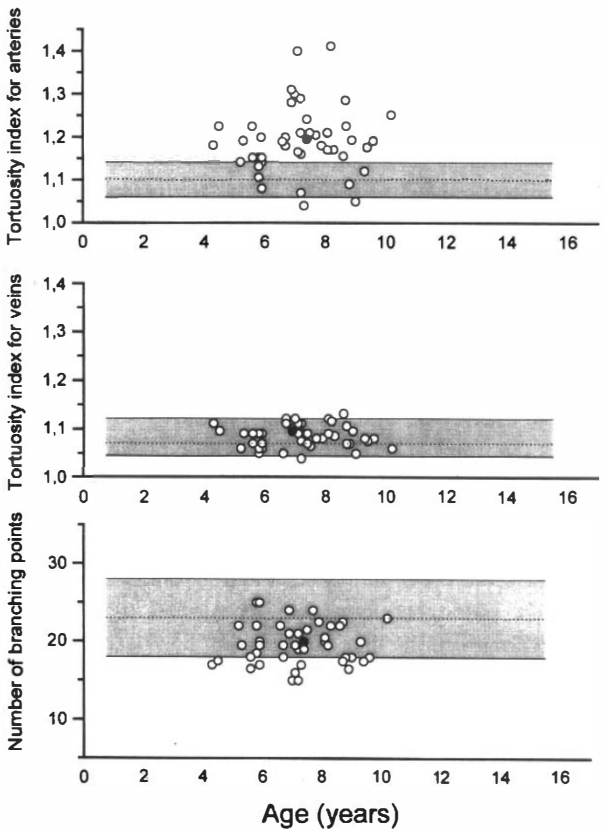

Fig. 3. *Index of tortuosity for arteries and veins, and number of vascular branching points in 45 children born very preterm. The shaded area depicts the 5th to the 95th centile range for the healthy reference group (tortuosity for arteries 1.06–1.14, tortuosity for veins 1.05–1.12 and number of branching points 18–28) and the centreline indicates the median for the healthy reference group.*[13] *The median for the preterm group is marked with a filled circle.*

All children had had cerebral ultrasonography performed during the perinatal period. Ten of them had intracranial haemorrhage (grade I–IV). These children were investigated by digital image analysis, which demonstrated a rim area below or equal to the median for the reference material in all 10 children. Three children had nystagmus; all of these children were fundus-photographed (2 under general anaesthesia), and all had a rim area below the median for the reference group.

Retinal vessel morphology

Abnormal retinal vessel morphology in the central fundus was common in the very preterm children (Fig. 3). This was expressed as increased tortuosity of the retinal arteries, independently of ROP, which has previously been reported in these children (median 1.19 vs 1.10 in controls; $p < 0.0001$).[17] Interestingly, 3 of the 5 children who had a tortuosity index below the median of the reference group had been cryo-treated for ROP and 1 child had growth hormone insufficiency.

In addition, the preterm children had a significantly higher tortuosity index for veins than the reference group (median 1.09 and 1.07, respectively; $p = 0.01$) and a significantly reduced number of vascular branching points compared with the reference group (median number 20 and 23 for children born preterm and the reference group, respectively; $p < 0.0001$).

The abnormal central retinal vascularisation was independent of the perinatal morbidity listed in Table 1.

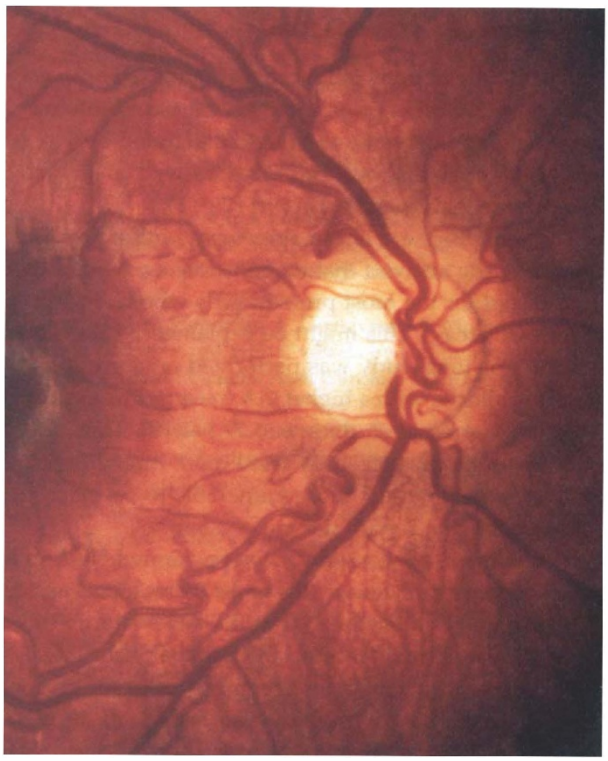

Fig. 4. *Fundus photograph of an 8-year-old boy, born at 24 weeks of gestation, demonstrating a pale temporal, normal-sized optic disc and an abnormal vascular pattern with tortuous retinal arteries and veins and a reduced number of vascular branching points.*

Ocular fundus diagnoses

One boy with hydrocephalus and PVL had markedly pale optic discs, diagnosed as optic atrophy. In addition, 1 child with attention deficit disorder and low scores on a visual perception test demonstrated, bilaterally, pale temporal portions of the optic nerves (Fig. 4). Eight children were classified as having hypoplastic maculae as determined by ophthalmoscopy and ocular fundus photographs. Three eyes in 2 children had signs of cicatricial ROP, manifested by temporal dragging of the retinal vessels.

Clinical ophthalmological examination

Altogether, 30 (60%) of the preterm children had some kind of visual abnormality, such as subnormal visual acuity, strabismus, impaired stereo vision, refractive errors and/or low scores on a test of visual perception. Two children (4%) were visually impaired according to visual acuity (WHO 1997); 19 of 50 children (38%) had significant refractive errors.[14]

Discussion

Independently of perinatal morbidity, children born very preterm (< 29 weeks of gestation) were found to have abnormal optic nerve morphology, illustrated by subnormal optic disc and rim areas, as well as an abnormal retinal vascular pattern (Fig. 1).

These findings are not in agreement with a previous morphometric analysis that demonstrated a normal disc area, except for the most preterm girls who had slightly larger disc areas.[9] This might be explained by the fact that the previous study was performed on a group of preterm children with a higher GA (mean 29 weeks) than those in the present study (mean 27 weeks). Thus, the children in the present study were more immature at birth and, theoretically, more vulnerable to perinatal influences on the central nervous system.

Maalouf and co-workers[18] have performed MRI on a group of preterm babies at 40 weeks (corresponding to full term) and demonstrated that the vast majority (n = 29) had an abnormal 'at-term' MRI appearance. This finding clearly demonstrates the influence of the change of environment on the preterm brain, which in the present study was reflected as smaller disc and rim areas. The smaller areas most likely reflect a reduced number of optic nerve axons, as experimental and clinical studies have indicated that the size of the disc, especially in small discs, is related to the number of axons.[19,20] Several studies have shown that children with a low birth weight as a group have suboptimal vision and/or an increased incidence of delayed visual maturation.[11,12] It may be speculated that a reduced number of optic nerve axons is one explanation for this, as all children who were investigated by digital imaging and who had suboptimal vision ($\leqslant$ 0.8) had a rim area below the median of the reference group.[13] In addition, it is interesting that a large proportion of the children with early neuro-imaging signs of brain lesions had subnormal optic disc and rim areas. In addition poor performance on the visual perceptual test was in some cases associated with subnormal rim areas (Fig. 1). Consistent with these findings, a few cases have been published demonstrating optic nerve hypoplasia among preterm children.[5,8]

While the full-term infant spends the last months of gestation in the relatively stable environment of the uterus, in which the growth spurt takes place, the preterm child spends the corresponding time period in a markedly different environment, with altered functional and metabolic requirements. At this stage of development (16–32 weeks of gestation), approximately two-thirds of the optic nerve axons are normally lost due to degeneration of supernumerary axons through apoptosis.[21] It has been suggested that interference with this process might cause excessive elimination of axons,[22] which thus could explain the subnormal optic disc and rim areas noted in the present study. In the present study, one boy with hydrocephalus and PVL was diagnosed as having optic nerve atrophy (large cups in normal-sized optic discs). However, in view of the early timing of the PVL lesion the optic disc finding may be regarded as optic nerve hypoplasia, as suggested by Jacobson and co-workers.[10] As discussed by Hoyt and Good,[23] there are difficulties in differentiating optic nerve hypoplasia from optic nerve atrophy. In the literature, the terms atrophy and hypoplasia have been used interchangeably, adding to the confusion of the definition of these disorders.

Experimental studies have shown that a lesion affecting the posterior visual pathways results in a trans-synaptic retrograde degeneration and loss of ganglion cells, which is much more pronounced in young animals (80%) than in adults (15%).[24] As PVL is a perinatal adverse event that, according to experimental studies, affects the number of axons in the optic nerve during a period when the system is not fully developed, it seems reasonable to adopt the term optic nerve hypoplasia.

In addition, an MRI study by Brodsky and Glasier[6] showed optic nerve hypoplasia among children with PVL. The pathogenetic mechanism for this morphological optic disc abnormality has been hypothesised to be due to retrograde trans-synaptic degeneration, as the primary ischaemic brain lesion in PVL causes axonal interruption in the optic radiation.[10] A recent report by Uggetti and co-workers[25] supports this hypothesis. They identified degeneration of the lateral geniculate nucleus as a possible consequence of trans-synaptic degeneration in an MRI study of 6 patients, 4 of whom had PVL.

The correction for magnification factors in preterm children has earlier been discussed since preterm children may have different causes for refractive errors compared with adults.[9] In preterm children the myopia is most likely caused by the abnormal eye development seen in these children, that is, a flatter anterior chamber and a thicker and more spheroid lens.[26–28] Thus, the correction methods used in adults should not be applied to the eyes of preterm children. To minimise the magnification errors in the present study only eyes with a refraction between +4 and –4 were included.

At a developmental stage when the fetus is immature and unprepared for extrauterine life the preterm child has to adapt to a high extrauterine oxygen tension. This may considerably alter the development of the vascular system, as suggested by the findings in the present study. The developing vasculature is under genetic and biochemical control. Several studies have shown that hyperoxia down-regulates vascular endothelial growth factor (VEGF), thereby inhibiting vascular progression.[29,30] This may lead to an avascular tissue, resulting in ischaemia, which would consequently stimulate VEGF and promote vessel growth. An altered environment may create altered trophic influences, i.e. changes in inhibitory and stimulatory mechanisms that may affect vessel morphology. This was seen in the present study, with increased tortuosity and a decreased number of vascular branching points.

Previous reports have demonstrated that the abnormal vascular pattern in preterm children is not seen at birth, but is developed around 2–3 months of age.[31–33]

This indicates that the postnatal environment may be responsible for the vessel abnormalities observed in preterm children.

What could be the consequences of the observed vascular abnormalities? There is reason to believe that the retinal vascular pattern noted in preterm children reflects similar changes in other vascular systems with similar architecture and autoregulation, i.e. the cerebral vessels, the coronary vessels and the vessels in the kidneys.[17] These are organs in which the vessel design and structure are of particular importance for nutrition and organ function.

Conclusion

Very preterm birth is associated with subnormal optic disc and rim area, tortuous retinal vessels in the central fundus and underdevelopment of the maculae. These findings clearly demonstrate the effect of preterm birth on the development of these structures. The long-term clinical prognosis of these findings has yet to be determined.

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