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National guideline for ophthalmological screening of premature infants in Germany (S2k level, AWMF guidelines register no. 024/010, March 2020)

Joint recommendation of the German Ophthalmological Society (DOG), German Retina Society (RG), Professional Association of Ophthalmologists in Germany (BVA), German Society of Pediatrics and Adolescent Medicine (DGKJ), Professional Association of Pediatricians (BVKJ), Federal Association "The Premature Infant", Society for Neonatology and Pediatric Intensive Care Medicine (GNPI)

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Guideline report

AWMF (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*) was founded in 1962 and is a network of 175 Scientific Medical Societies in Germany. AWMF is the national member for Germany in the Council for International Organizations of Medical Sciences (CIOMS) at WHO, Geneva.

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Involvement of other participating medical societies/organizations

- German Retina Society (RG)
- Professional Association of Ophthalmologists in Germany (BVA)
- Professional Association of Pediatricians (BVKJ)
- Federal Association "The Premature Infant"

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Mandating

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- Prof. Dr. Claudia Roll for the GNPI and DGKJ
- Prof. Dr. Andreas Stahl for the DOG

Scope and purpose

- Rationale for guideline topic selection: to ensure the timely diagnosis of all cases of retinopathy of prematurity (ROP) requiring intervention
- Goals of this guideline: to establish evidence-based and rational recommendations for screening of ROP in preterm infants, while avoiding over- and under-diagnosis
- Patient target population: preterm infants at risk for ROP
- Area of health care: screening, specialized and primary care, inpatient and outpatient pediatric and ophthalmology centers
- Target user group/addressees: pediatricians, ophthalmologists

Members and authors of the guideline working group

- participating professional groups
  - Pediatricians in the inpatient and outpatient sector
  - Ophthalmologists in the inpatient and outpatient sector
- patient advocacy groups
  - Involvement of the Federal Association "The Premature Infant" as a patient representative

Methodological rigor

Search, selection, and critical appraisal of scientific evidence

- Key questions
  - Target groups: i.e. which infants need ROP screening?
  - When should the first examination be performed?
  - At what intervals should follow-up examinations be performed?
  - When can ROP screening be discontinued?
  - What is the examination procedure?
  - How should ophthalmologic findings be classified and documented?
  - Which findings should prompt treatment intervention?
- Using existing guidelines on the topic
  - First edition of this guideline published in 1999 (see below)
  - Second edition of this guideline published in 2007 (see below)
  - British guideline published in 2008
  - Dutch guideline published in 2013
  - Swedish guideline published in 2012
  - US guideline published in 2018
  - Canadian guideline published in 2006
- Systematic literature search
  - PubMed (focusing on 2000–2019, particularly relevant literature, including older publications), using the MeSH term "retinopathy of prematurity" alone and in combination with other terms such as "VLBW infants," "screening," "ophthalmological examination," "fundoscopy," "guideline," "recommendation"
  - Other results from manual searches in selected medical journals of interest and reference lists in the literature found

Abbreviations

Glossary

Additional findings to be documented	Neovascularization of the iris (in severe ROP), hyperemia of the iris (increase in visible, dilated vessels in the iris), vitreous haze and floaters, retinal and/or vitreous hemorrhage, moderate pharmacological pupil dilatation.
Aggressive posterior ROP (AP-ROP)	Changes in the region of the posterior pole that, if left untreated, generally progress to stage 5. Characteristic changes: posterior location in zone I or in posterior zone II, marked plus disease (formerly referred to as rush type disease). Disproportionately greater vascular filling and tortuosity in all four quadrants compared to peripheral changes. Shunt vessels between retinal vessels not only in the region of the border of vascularization, where bleeding is possible. Changes do not progress through the normal stages. Flat network of neovascularization at the indistinct boundary between vascularized and non-vascularized retina (easily overlooked). AP-ROP typically extends circumferentially.
Gestational age (GA)	Age at maturity: expressed in full weeks of gestation and days from the 1st day of the last menstrual period (e.g., 28 weeks +5 days = 28 + 5 weeks GA).
Immature retina	Incomplete retinal vascularization in the absence of ROP. It is essential here to specify the zone into which vascularization extends.
Plus disease	Vascular dilatation and tortuosity at the posterior pole of the fundus in at least two quadrants.
Postmenstrual age	Gestational age plus postnatal age (the term "postconceptional" is often used in error).
Postnatal age	The time elapsed after birth.
Pre-plus disease	Vascular changes at the posterior pole that do not yet meet the criteria for plus disease.
Threshold disease	Moderately severe extraretinal proliferations over at least five contiguous or eight non-contiguous clock-hours in zone II in conjunction with plus disease.
Tunica vasculosa lentis anterior (TVL)	A vascular membrane that covers the anterior lens capsule (membrana epipupillaris) during fetal life. When TVL is dilated and has a greater number of tortuous vessels, this is a sign for active ROP.

Additional information
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Formulation of the recommendations and structured consensus finding

- Formal consensus development techniques: procedure and implementation
  - Email-based group discussion process with participants holding a mandate from their respective societies/interest groups
  - Literature searches on questions raised, followed by one anonymized (03/06–15/04/2019) and two open email-based Delphi rounds (GNPI Delphi Conference)
  - The final draft was unanimously accepted with all recommendations (strong consensus [> 95% of eligible voters]) according to AWMF policy
- Consideration of benefits, side effects, and relevant outcomes
  - The benefit for infants as well as for society is related to the prevention of blindness.
- Formulation of recommendations
  - Based on the current state of the literature, the previous version of the guideline was revised and a new draft was written by the lead author to be modified by the participating co-authors.
- The final wording is the result of several revision steps, which also involved a large number of conference calls between the authors.
- According to AWMF regulations, the strength of recommendation is expressed by using the verbs "shall" (strong recommendation), "should" (recommendation), and "can" (open recommendation).

External review and adoption

Piloting

The two previous editions of this guideline can be regarded as pilot tests.

External review

Experience with previous editions of the guideline was a key factor for drafting the current version. Another key factor was the above-mentioned Delphi process serving for critical appraisal, discussions and shared decision making.

Adoption by the chairpersons of the publishing medical societies/organizations

Unanimously adopted by the GNPI Executive Board on 09.03.2020, subsequently approved by the other contributing societies and the German Federal Association "The premature infant" e. V. (by 10.05.2020).

Dissemination and implementation

Concept for dissemination and implementation

This guideline shall be published in the relevant pediatric and ophthalmological literature in addition to the AWMF guideline register and the GNPI homepage.

Supporting materials for guideline application

The guideline contains two forms for documentation of ophthalmologic findings that can be utilized by users: one form for the documentation of findings, as well as one form ("ROP passport," which can be included in the infant's screening booklet) for the documentation of surgical interventions undertaken at the ocular fundus and scheduled follow-up visits.

Discussion of possible organizational and/or financial barriers to the use of the guideline recommendations

Barriers and opposition to the examinations recommended in the guideline are not anticipated.

Monitoring criteria: quality objectives, quality indicators

Screening for retinopathy of prematurity is part of the nationwide mandatory quality assurance measures in neonatology. The indication-based and timely performance of retinopathy screening and its results are annually recorded in all perinatal centers and centrally evaluated and published within the framework of a national quality assurance program (German Institute for Quality Assurance and Transparency in Health Care, IQTIG).

Period of validity and update procedure

- First edition (024–010.01): 06/1998
- First revision (024–010.02): 11/2007
- Current edition (024-010.03): 03/2020
- Next revision scheduled in: 03/2025

Main changes as compared to the previous version

This guideline replaces the first edition published in 1999 [6] and its first update in 2008 [33]. Compared to the previous edition, the following specific points were changed:

- The gestational age limit for inclusion in routine screening for ROP was lowered from $< 32 + 0$ weeks to $< 31 + 0$ weeks gestational age (GA) at birth.
- The indication for screening in more mature preterm infants ($\geq 31 + 0$ weeks) was modified.
- The indications for treatment have been extended; specifically treatment in stage 3+ in zone II is now considered for neovascularization in fewer than five contiguous or eight non-contiguous clock-hours.
- The new version of the screening guideline includes, for the first time, a paragraph on treatment with VEGF inhibitors, to the extent that this is relevant for screening.
- Criteria for the duration of screening following anti-VEGF therapy were introduced.
- This guideline provides a "ROP passport" that should be used to document all steps of of ROP treatment, follow-up examinations after ROP treatment, in particular after anti-VEGF therapy (**Fig. 4**).

For details on the treatment of ROP, the reader is referred to the statement of the ophthalmological societies on laser and anti-VEGF therapy of retinopathy of prematurity.

Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is caused by impaired retinal vascular development due to premature birth. If left untreated, this disease can lead to blindness, an outcome that can be largely prevented by local treatment if early stages of the disease are detected in a timely manner. Therefore,

Table 1 Incidence (absolute and in percent) of ROP in preterm infants weighing less than 1500 g at birth in Germany in 2017 [30]

Gestational age (GA, completed weeks)	22	23	24	25	26	27	28	29	30	31	≥ 32	All GA
Stage 1 (*n*)	≤ 3	29	92	112	129	173	156	140	95	44	21	992
(%)	*3.70*	*14.95*	*19.05*	*20.44*	*18.48*	*20.69*	*14.63*	*12.48*	*9.60*	*6.49*	*3.99*	*13.84*
Stage 2 (*n*)	10	46	125	121	122	104	87	40	24	7	6	692
(%)	*37.04*	*23.71*	*25.88*	*22.08*	*17.48*	*12.44*	*8.16*	*3.57*	*2.42*	*1.03*	*1.14*	*9.65*
Stage 3 (*n*)	10	76	135	93	63	19	23	10	6	≤ 3	≤ 3	439
(%)	*37.04*	*39.18*	*27.95*	*16.97*	*9.03*	*2.27*	*2.16*	*0.89*	*0.61*	*0.29*	*0.38*	*6.12*
Stage 4 (*n*)	≤ 3	5	≤ 3	≤ 3	≤ 3	≤ 3	0	0	0	0	0	11
(%)	*3.70*	*2.58*	*0.62*	*0.18*	*0.14*	*0*	*0*	*0*	*0*	*0*	*0*	*0.01*
Stage 5 (*n*)	0	≤ 3	0	0	0	0	0	0	0	0	0	0.00
(%)	*0*	*0.27*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0.01*
Surgery* due to ROP (*n*)	7	45	68	30	28	5	7	4	≤ 3	0	0	196

*Surgery = Laser therapy or cryotherapy (*n* = 79) or anti-VEGF injection (*n* = 118) or other surgery (*n* = 35)
For data protection reasons, case numbers ≤ 3 are not broken down in the statistics.

Table 2 Staging according to the International Classification of ROP (ICROP) [29, 76, 78]

Stage 1	Demarcation line
Stage 2	Ridge
Stage 3	Ridge and extraretinal fibrovascular proliferation
Stage 4a	Partial retinal detachment without macular involvement
Stage 4b	Partial retinal detachment with macular involvement
Stage 5	Total retinal detachment

systematic screening is required in very preterm infants.

Special features of the eye in preterm infants

Both cornea and vitreous may still be cloudy in the early postnatal phase of very preterm infants, which can significantly impair or completely prevent visualization of the retina. Fetal vessels in the iris and around the lens are often still visible in premature infants, regressing as they mature [22]. The pupils of very preterm infants have a diameter of approximately 3–3.5 mm and, as part of development, usually do not yet have a light reflex at a gestational age of less than 30 weeks, whereas this reflex is regularly detectable from 35 weeks GA onwards [63].

Pathogenesis of retinopathy of prematurity

ROP is caused by impaired vascularization of the retina. Vascularization occurs physiologically between 16 and 40 weeks of gestation in the form of vasculogenesis and angiogenesis while the fetus is still in the intrauterine environment [28]. With 27 weeks, approximately 70% of retinal blood vessels have developed. Premature birth, with the onset of pulmonary gas exchange, causes a rapid increase in oxygen saturation far above intrauterine levels (and lead to oxygen availability too high for gestational age = relative hyperoxia), which suppresses the expression of hypoxia-regulated genes. These include, for example, vascular endothelial growth factor (VEGF). VEGF is an essential growth factor for proliferating endothelial cells and endothelial progenitor cells. Reduced VEGF production due to the relative hyperoxia after birth initially causes inhibition of retinal vascular development in the early phase of ROP development. From 32–34 postmenstrual weeks, a second phase of ROP development begins. With the onset of retinal maturation and the associated increased oxygen requirement, the lack of retinal vascular development results in relative hypoxia, which leads to increased hypoxia-inducible factor (HIF-1 alpha) and subsequently to local release of VEGF and other proangiogenic factors within the retina. While VEGF at physiological levels is required for proper retinal vascular development, at excessive levels it causes pathological, aberrant retinal neovascularization. This neovascularization may extend beyond the level of the retina, grow into the vitreous, and be accompanied by formation of myofibrils. The contraction of these myofibrils can cause partial or complete tractional retinal detachment, thereby causing (partial or full) loss of vision as the disease progresses further. In addition to regulating vascular development through hyperoxia and hypoxia, the insulin-like growth factor (IGF-1) that is synthesized in the liver plays an important modulatory role [21, 70]. In the setting of malnutrition, low weight gain, necrotizing enterocolitis, and sepsis, IGF-1 is reduced, resulting in an increased risk of developing ROP [21, 45]. However, IGF-1 replacement does not seem to prevent the development of ROP [43].

Supplemental oxygen delivery at the pre-threshold stage of ROP (i.e., the transition from delayed to reactivated retinal angiogenesis) did not significantly reduce the progression of ROP [44, 74].

Risk factors for retinopathy of prematurity

The most important risk factor is the infant's degree of immaturity at birth. In pathophysiological terms, the partial pressure of oxygen plays a crucial role in the early postnatal period. However, the optimal oxygen tension/saturation for very preterm infants during the first weeks of life remains unclear: Goals are both, to avoid

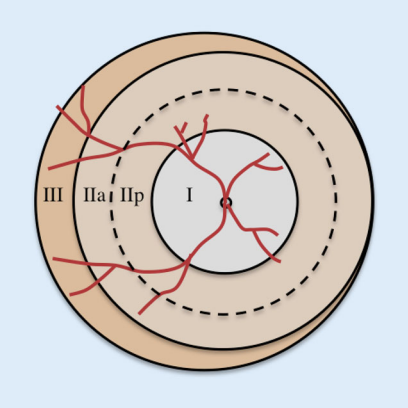


Fig. 1 ▲ Zone designation according to the International Classification of ROP (ICROP) [29, 76, 78]. Zone I: The central retina within a circle around the optic disc with the radius being twice the distance from the optic disc to the fovea. The fovea is poorly defined in very preterm infants. If it is possible—by using a 28-diopter (D) condensing lens—to simultaneously visualize the optic disc nasally and see the border of vascularization temporally, zone I disease is present [29]. Zone II: The midperipheral retina peripheral to zone I within a circle with the radius being the distance from optic disc to nasal ora serrata. Posterior zone II is defined as the area delineated by a circle around the optic disc measuring three times the distance between optic disc and fovea (*dashed line* in the figure). This definition (measured on the temporal side) was used in the BEAT-ROP trial [52]. The results in the BEAT-ROP study for zone II refer exclusively to this posterior region. Since posterior zone II and zone I have similar pathophysiological implications suggests that, in the case of zone II ROP, differentiating between posterior and anterior zone II may be clinically important. Zone III: The remaining peripheral retina on the temporal side outside zone II

hyperoxemic tissue injury and to avoid hypoxemia and its sequalae and thus to ensure healthy survival: the risk of developing ROP seems to be lower with target pulse oximetry oxygen saturation levels of 85–89% as compared to 91–95%. However, the risk for both, mortality and necrotizing enterocolitis appears to be higher with the lower target range [3, 67, 69, 75].

Other factors reported to be associated with the development of higher-grade ROP include intrauterine growth retardation [48], poor postnatal weight gain [87], formula feeding rather than breastfeeding [50, 71], thrombocytopenia with infections [49, 82], systemic fungal infections [2], parenteral feeding without added polyunsaturated fatty acids [1], hemodynamic stress in the first months of life [12], and hypoxemic episodes from the second month of life [14]. Genetic disposition also appears to play a role [55, 57]. For example, certain variants in the brain-derived neurotrophic factor (BDNF) gene are associated with an increased risk for a higher degree of ROP [20].

Incidence of retinopathy of prematurity

In Germany, every year approximately 65,000 infants are born preterm, of whom approximately 12,000 undergo ROP screening (as of 2018). These numbers have risen steadily in recent decades [40, 41]. However, detection and classification of ROP also depends on the experience of the examining ophthalmologist. ◘ **Table 1** shows the incidence of preterm infants with various stages of ROP as documented in the neonatal population based survey conducted in Germany in 2017. Staging of the disease reported here relates to the highest stage of the disease observed in each individual infant, regardless of treatment performed.

Clinical course of retinopathy of prematurity

The clinical course of the disease follows a characteristic sequence:

1. A latency phase lasting several weeks between birth and onset of the disease visible by fundus examination
2. An acute phase occasionally with rapid progression of the condition, sometimes requiring timely treatment
3. Spontaneous remission in most cases that do not require treatment [11, 58, 62, 68]

Without appropriate intervention, certain stages require treatment to avoid complete blindness (for staging see ◘ **Table 2**, and for zone designation of the fundus see ◘ **Fig. 1**). Even with correct and timely treatment, unfavorable outcomes may occur, depending on ROP progression. The frequency and severity of unfavorable outcome depends heavily on the baseline findings prior to treatment. The CRYO-ROP study found unfavorable outcome in 50% of eyes with stage 3+ ROP in zone II, and in as many as over 90% of cases of stage 3+ ROP in zone I, despite cryotherapy [9, 10]. Although these unfavorable courses of the disease do not necessarily lead to blindness, they do involve permanent structural changes such as macular distortions or folds, which may result in a severe reduction in visual acuity.

Indications for retinopathy of prematurity screening

The goals of ROP screening are to identify all preterm infants whose retinopathy reaches a stage requiring treatment and to treat these infants adequately and according to stage. Since screening examinations require significant time and ressources, and impose an additional burden of discomfort on preterm infants, the initial examination should not be done before a certain postmenstrual age, and reasonable intervals for follow-up examinations should be chosen. Unnecessary and unnecessarily early examinations should be avoided. Additional, non-invasive investigations, such as natriuretic peptides in urine [12] and/or risk scores [48, 87], may help to reduce the number of screening examinations in the collective at low risk for ROP in the future.

Although a number of other countries with highly developed health care systems have an upper gestational age limit for mandatory screening (irrespective of the presence of risk factors) of under 31 + 0 weeks GA or even under 30 + 0 weeks GA (an overview of international guidelines is provided in ◘ **Table 3**), the limit in the previous edition of the German guideline has been < 32 + 0 weeks GA [33]. However, an analysis of data from the German Retina.net ROP Registry (www.rop-register.de) revealed that of 281 children treated for ROP in the 2011–2018 birth cohorts recorded in the registry, not one single preterm infant had a gestational age within the range of 31 + 0 to < 32 + 0 weeks, indicating that, likewise in Germany, this group apparently has a very low risk of developing ROP requiring treatment. However, this group accounts for a significant proportion of the overall screening population in Germany to date [41]. Therefore, in order to increase the specificity of screening and to avoid

Table 3 Indications for ROP screening in international guidelines

Land	Gestational age limit for mandatory ROP screening	Additional criteria for ROP screening	Publication year	Reference
United Kingdom	< 31 weeks ("must") < 32 weeks ("should")	< 1251 g ("must") < 1501 g ("should")	2008	[85]
Sweden	< 31 weeks (< 30 weeks)	–	2012 (Proposal 2019)	[23] [25]
The Netherlands	< 30 weeks	< 1250 g In case of risk factors: < 32 weeks or < 1500 g	2013	[81]
Canada	< 31 weeks	Higher gestational age in case of risk factors	2006	[35]
USA	< 31 weeks	< 1500 g Higher gestational age in case of risk factors	2018	[16]

unnecessary screening exminations, the upper limit for mandatory screening (irrespective of the presence of risk factors) has now been lowered in this guideline revision from previously < 32 + 0 to now < 31 + 0 weeks GA.

ROP screening is indicated in:

- Preterm infants with < 31 + 0 weeks GA (or < 1500 g birth weight if gestational age is not reliably known) irrespective of supplemental oxygen administration [16, 23, 24, 35, 62, 85].
- All preterm infants (i.e., all neonates with a gestational age of less than 37 + 0 weeks GA) who, at the discretion of the treating neonatologist, are at risk of developing ROP, for example, due to:
  - Postnatal supplemental oxygen administration for more than 5 days or ECMO therapy [42]
  - Relevant comorbidities (e.g. severe necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, anemia requiring transfusion)

The assessment and documentation of retinal findings is carried out according to the ICROP classification, as shown in **Table 2** and **Fig. 2** [29, 76, 78]. Gestational age-based limits for mandatory ROP screening from national guidelines in other countries are summarized in **Table 3**.

Timing of the initial, follow-up and termination of screening examinations

Initial examination

As a general rule, the first eye examination should be performed in the 6th postnatal week (36th–42nd day of life), but not prior to a postmenstrual age of 31 + 0 weeks.

Current evidence suggests that even in extremely preterm infants, the initial examination at 31 + 0 postmenstrual weeks is sufficiently early [16, 51].

Follow-up examinations in infants without prior ROP treatment

As a basic principle, screening examinations in untreated ROP shall be performed at *2-week* intervals, unless one of the following situations occurs:

- when the border of vascularization is in zone I or posterior zone II (irrespective of the presence of ROP), or
- when the border of vascularization is in anterior zone II in stage 2 or 3 ROP, or
- In all cases of ROP with plus disease.

In these situations, the interval for follow-up examinations shall be reduced to *1-week* intervals, and depending on disease progression, intervals of even less than 1 week may be appropriate in individual cases, e.g., in rapidly progressive ROP or very immature retina.

The interval for follow-up examinations can be extended to *3-week* intervals when:

- The border of vascularization is in zone III in the absence of ROP

The follow-up interval specified in each case can be *extended by 1 further week* if:

- An improvement in findings is observed over several examinations.
- The estimated (calculated) date of birth has already been passed.

The criteria for ending screening or for performing treatment are defined in the following chapters.

It is recommended that the treating hospital arrange the first post-discharge appointment for the patient with an ophthalmologist with significant experience in ROP.

Discontinuing screening without having performed treatment

Screening for acute ROP can be discontinued in cases without any specific treatment when:

- The peripheral retina is fully vascularized circumferentially, or
- A clear regression of peripheral retinal changes associated with acute ROP can be seen, but only once the calculated date of birth has been passed.

More recent studies show that severe ROP can develop even after discharge from inpatient care [37]. Therefore, these recommendations apply irrespective of whether an infant is still hospitalized or has already been discharged.

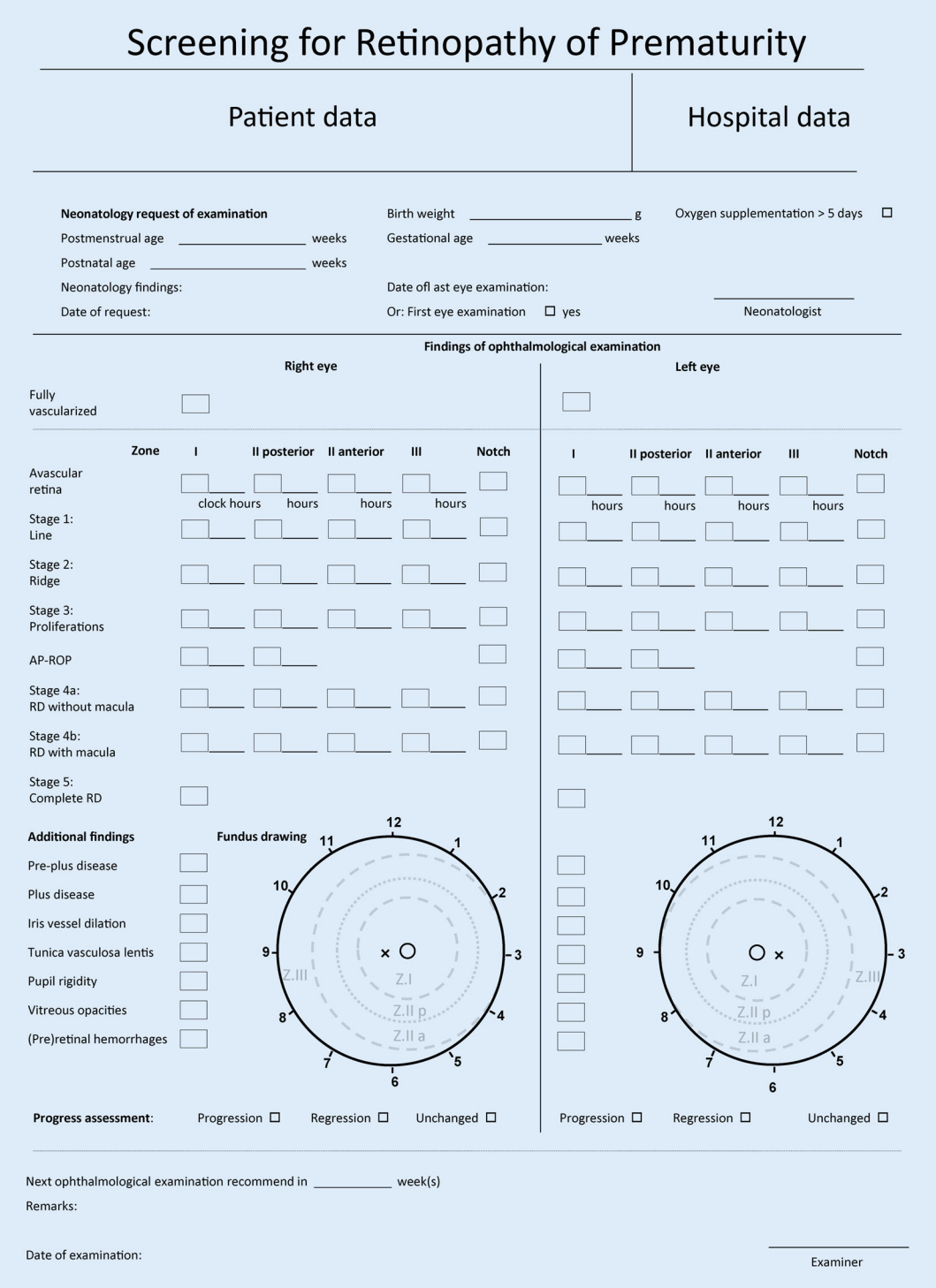


Fig. 2 ◀ Documentation form for retinopathy screening

Treatment of retinopathy of prematurity

General remarks

A variety of interventions are available for the treatment of ROP. Apart from exceptional cases, treatment consists of retinal laser coagulation or intravitreal anti-VEGF therapy. For the selection of treatment method, the reader is referred to the statement of the medical ophthalmological societies. The available intravitreal anti-VEGF drugs, with the exception of ranibizumab (Lucentis®), are currently not approved for use in ROP, and are used currently "off label."

Based on published interventional trial results the following indications for the treatment of ROP with retinal laser coagulation or intravitreal anti-VEGF therapy are suggested:

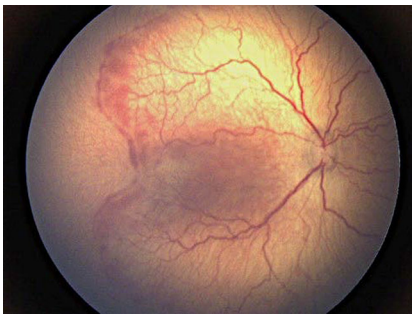


Fig. 3 ▲ Temporal notch. Temporally delayed vascularization in the region of the raphe with more central border of vascularization in the area of the notch. The findings shown here represent an indication for treatment since extraretinal proliferations can be seen (posterior zone II stage 3+ with temporal notch)

- In zone III disease, treatment is generally not necessary, even in the presence of plus disease (vascular dilatation and tortuosity) [8, 58].
- In zone II disease, treatment is indicated at latest when stage 3 is observed in five contiguous or eight noncontiguous clock-hours in conjunction with plus disease at the posterior pole of the eye (referred to as threshold disease) [8]. Earlier treatment of zone II stage 3+ (as early as when only one clock-hour is affected) may be beneficial as well.
- In zone I disease, treatment is indicated when plus disease is present (irrespective of ROP stage) or in the case of stage 3 disease (irrespective of the presence of plus disease) [77].
- Furthermore, urgent treatment is indicated in the case of aggressive posterior ROP (AP-ROP) in zone I or posterior zone II. As the disease may progress rapidly, treatment should be initiated as soon as possible (sometimes within 24 h of diagnosis).

Delayed vascularization of the temporal retina in the region of the raphe with temporal notch of the border of vascularization of less than two clock-hours (◘ **Fig. 3**) does not determine zone designation. Rather, zone designation (and treatment indication where applicable) is based on the border of vascularization outside the area of the temporal notch.

As a general rule for treatment decision making, one should consider that spontaneous regression from ROP stage 1 or 2 is seen in the vast majority of eyes with ROP. On the other hand, if the disease reaches a stage requiring treatment as indicated above, an unfavorable outcome has been reported in 50–90% of cases, depending on the stage of the disease. Treatment can significantly improve this prognosis. However, if treatment is not performed until disease is advanced (e.g., to stage 4), success rates are significantly lower. Since acute ROP stage 3 may progress to stage 4 or 5 rapidly, prompt intervention is very important for successful treatment. A treatment delay of only a few days may result in treatment failure.

When treatment is indicated based on the above criteria, an ophthalmologist should decide how urgent treatment is required. Usually treatment shall be performed within a few days. However, particularly in the case of rapid progression, urgent treatment may be required. For this reason, the timeline of the treatment under consideration must be coordinated between the neonatologists, anesthesiologists, and opthalmologic surgeons in charge for the preterm infant, and discussed with the parents in a timely fashion.

Methods available for treatment of retinopathy of prematurity

Cryotherapy

Since comparative studies [7, 56, 59] have shown that the anatomical and functional treatment outcomes of laser therapy are superior to cryocoagulation [8–10], the latter is performed nowadays only in exceptional situations.

Laser therapy

Laser therapy in defined stages of the acute phase offers an established treatment method that is able to reduce the incidence of unfavorable outcomes [79]. Laser coagulation is generally performed exclusively in areas of avascular retina [32, 59, 79].

Intravitreal injection of anti-VEGF therapy

Intravitreal injection of VEGF inhibitors has been investigated as a new treatment option for a number of years [66]. However, only a few randomized controlled trials on the efficacy and safety of anti-VEGF antibodies are currently available. The two randomized trials available to date showed anti-VEGF therapy to be superior to laser therapy in terms of structural outcome [52, 73].

Following anti-VEGF therapy, retinal vessels may continue to grow in the peripheral retina, whereas laser coagulation therapy induces areas of scarring at the site of treatment. However, after initial anti-VEGF therapy, laser therapy may become necessary if the disease progresses further.

The medium-term results available to date for follow-up examinations after anti-VEGF therapy suggest a lower rate of severe myopia [17] compared to laser therapy, with comparable visual acuity [31]. However, questions remain related to drug selection and dosage. Only bevacizumab (Avastin®) [5, 52] and ranibizumab (Lucentis®) [5, 72, 73] have been investigated in randomized controlled trials at this time. For conbercept and aflibercept (Eylea®), only individual case reports and retrospective case series without a control group are available [27, 36, 65]. Whereas initially half the adult dose was used [52], more recent studies indicate that lower doses may result in a sufficient treatment effect [15, 19, 47, 72, 83].

It is unclear to what extent the intravitreal administration of VEGF inhibitors can cause systemic side effects in preterm infants [18, 80]. Systemic absorption and serum VEGF suppression have been shown for bevacizumab at up to 3 months after intravitreal injection [39, 89]. More recent studies suggest that this systemic suppression of VEGF appears to be lower or undetectable when ranibizumab is used [72, 73, 89].

Arterial hypotension has been described as a short-term side effect following anti-VEGF therapy [88]. Only very limited and conflicting data is available on long-term psychomotor development of infants after anti-VEGF therapy [38, 54].

For the consideration of whether to use laser or anti-VEGF therapy, the reader is referred to the respective statement of the medical ophthalmological societies.

Surgical retinal procedures

In selected cases with advanced ROP stage (stages 4 and 5), prompt retinal surgery such as vitrectomy and/or scleral buckle surgery at a retinal surgery center may be beneficial. However, functional outcomes are significantly poorer compared to successful treatment at earlier stages of ROP.

Treatment documentation

To document treatment course following any type of therapy, all treatment providers are invited to participate in the nationwide German Retina.net ROP register (www.rop-register.de). This nationwide register of individual treatment courses will be useful to answer open questions in ROP treatment.

Follow-up examinations after treatment for retinopathy of prematurity

The follow-up examinations after laser therapy and after anti-VEGF therapy differ significantly.

Follow-up examinations after laser therapy

Initially follow-up is done at least in weekly intervals until disease activity has reliably regressed and to ensure that all avascular areas have been sufficiently lasered. Thereafter, intervals can be extended until retinal findings are stable and there is no active proliferation, no active retinal traction, and no plus disease. Complete vascularization of the peripheral retina is not possible following successful and complete laser therapy, and should therefore not be expected.

Follow-up examinations after intravitreal anti-VEGF therapy

Following intravitreal injections, prompt postoperative follow-up is mandatory to exclude injection-related complications, particularly endophthalmitis. Thereafter, follow-up intervals depend on ROP severity. Intervals can be selected based on activity and the zone in which the border of vascularization is located, as described above ("Follow-up examinations in untreated ROP"), with the crucial difference that follow-up for considerable time after discharge is usually necessary well beyond the calculated date of birth [53], as late recurrences requiring additional treatment may occur [26, 34, 40, 86].

To ensure adequate follow-up of ROP cases after discharge of the premature infant, all physicians and other caretakers involved need to be aware of the individual need for ophthalmological follow-up examinations, all relevant medical data (e.g., date and findings of the last examination, recommended date of the next examination). Written information shall be shared with the ophthalmologist and the pediatrician providing continuing care. This may be done using the so called "ROP passport" (see Appendix), which can be added into the infant medical screening booklet and/or to the follow-up passport for premature infants used by some caretakers in Germany (**Fig. 4**).

Final follow-up examinations once anti-VEGF therapy has been performed

Follow-up after anti-VEGF therapy can be discontinued once:

- The retina is fully vascularized, or
- Residual areas of peripheral retinal avascularity have been fully treated with additional laser therapy and there are no signs of vascular activity requiring treatment, such as plus disease and/or proliferation, or
- Findings over several months have included residual avascular retinal areas but no pathological vascular activity. Recurrent disease has been described in some cases up to a postmenstrual age of 69 weeks or 35 weeks after the last intravitreal injection [34, 86].

Performing eye examinations

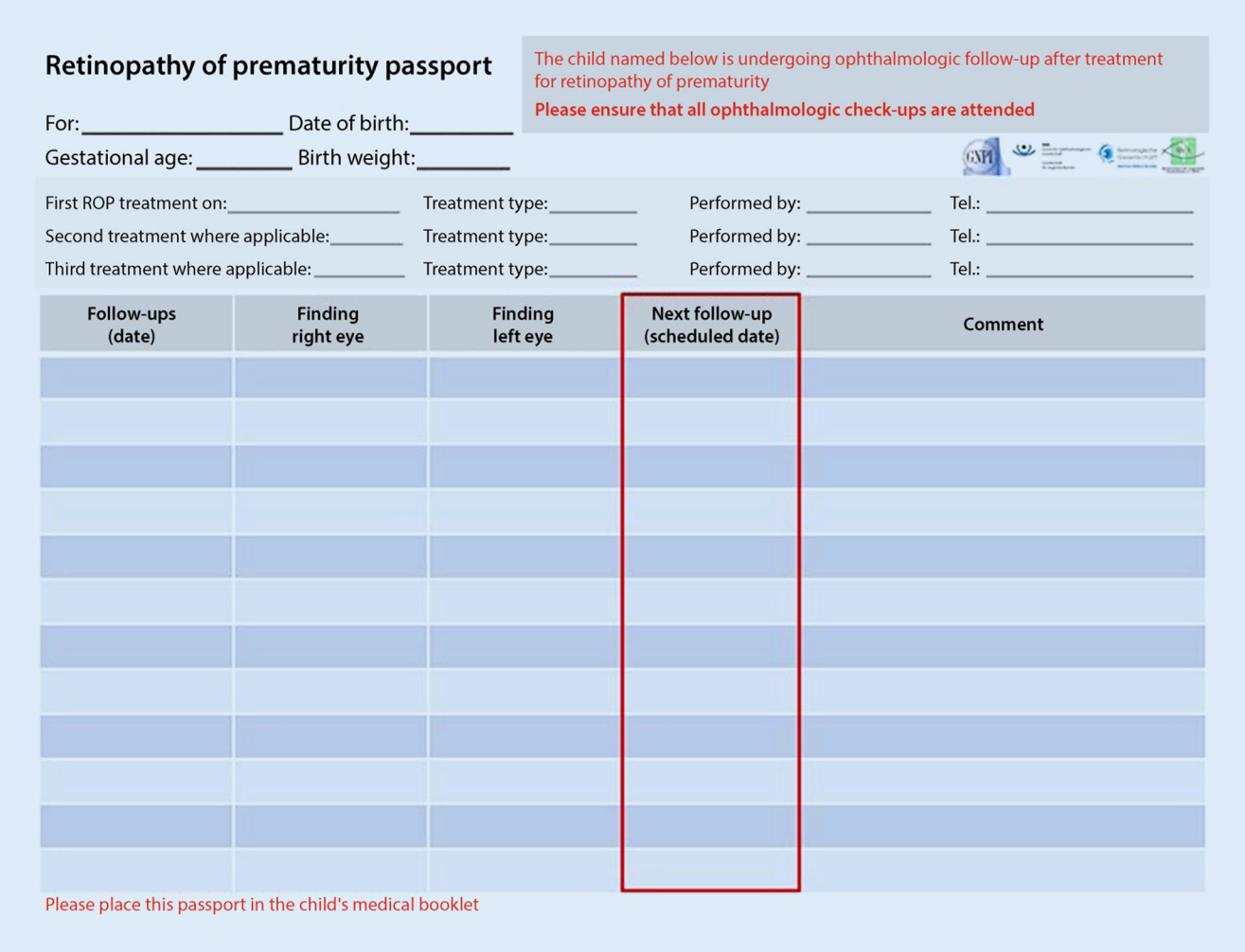
Requirements on the ophthalmological examiner

Ophthalmologists carrying out ROP screening and subsequent follow-up after treatment must have previous experience with examination of preterm infants, indirect ophthalmoscopy, as well as with the diagnosis and classification of ROP. When imaging techniques such as wide-angle photography are used for the examination, the photographer must have particular experience in visualizing the ocular fundus, including the periphery, in order to capture all possible pathologies. In cases of critical disease in whom the indication for treatment is unclear, the images shall be evaluated by an expert in ROP ideally on the same day, and definitely within 24 h for all patients, to ensure adequate visualization of the retina by imaging and interpretation of the images.

Preparing and performing the examination

The following prerequisites shall be met for a reliable assessment of disease:

- Maximum possible pharmacological pupil dilation (mydriasis) by timely and sufficient application of appropriate eye drops into the conjunctival sac, e.g., tropicamide 0.5% and phenylephrine 2% or atropine 0.1%. Attention should be paid to possible systemic side effects of mydriatic agents, but adequate mydriasis is the key for reliable assessment and diagnosis.
- In order to examine the infant, a second person is required (e.g., a member of the nursing staff) to hold the infant and stabilize the infant's head. When caring for preterm infants on the neonatal intensive care unit (NICU), a member of the NICU nursing staff shall be immediately available at all times. Since examining the infant in a closed incubator can limit the examiner's ability to assess the retina, the benefits and risks of opening the incubator should be balanced individually.
- Application of local anesthetic eye drops in the conjunctival sac before placing a blepharostat or eyelid retractor.
- To reduce pain, non-pharmacological measures, such as non-nutritive sucking or oral glucose [61], should be used alongside local anesthesia [13].
- Binocular ophthalmoscopy enables the examiner to rotate and indent the eye globe in addition to making a stereoscopic evaluation of the ocular fundus. This examination shall ensure reliable visualization of the border of vascularization. When the latter



Retinopathy of prematurity passport

The child named below is undergoing ophthalmologic follow-up after treatment for retinopathy of prematurity

Please ensure that all ophthalmologic check-ups are attended

For:_____ Date of birth:_____

Gestational age:_____ Birth weight:_____

First ROP treatment on:_____ Treatment type:_____ Performed by:_____ Tel.:_____

Second treatment where applicable:_____ Treatment type:_____ Performed by:_____ Tel.:_____

Third treatment where applicable:_____ Treatment type:_____ Performed by:_____ Tel.:_____

Follow-ups (date)	Finding right eye	Finding left eye	Next follow-up (scheduled date)	Comment

Please place this passport in the child's medical booklet

Fig. 4 ▲ ROP passport to be placed in the infant's medical screening booklet or in the follow-up care passport for preterm infants

is located peripherally, the use of an indenter is required.
- The use of a wide-angle camera allows to document [46, 60, 64] as well as telemedically assess findings by other experts [46, 84], which may be particularly useful given that individual assessments can vary [4]. Again, reliable visualization of the border of vascularization is crucial.

Examination procedure

A standardized examination procedure is recommended for screening examinations:
- Assessment of the anterior eye segment: pupil size, persistent tunica vasculosa lentis, hyperemia of the iris, neovascularization of the iris, posterior synechia, cataract, vitreous haze and/or floaters. Features including hyperemia of the iris, neovascularization of the iris, and dilated vessels within persistent tunica vasculosa lentis are usually indicators of an advanced stage of ROP requiring treatment.
- Assessment of the central retina, including border of vascularization, plus disease, distortion of retinal vessels (narrowed angle between the temporal major vascular arcades), retinal detachment, vitreous condensations, retinal traction.
- Assessment of the peripheral retina in a circumferential direction: border of vascularization, severity and extent of ROP including extraretinal and/or flat intraretinal neovascularization and/or vitreous hemorrhage, vascular tortuosity, vasodilation, retinal detachment.
- Classification and documentation of the recorded findings according to the International Classification (◘ **Table 2**, ◘ **Fig. 2**; [29, 76, 78]): location (zone), extent (clock-hours), stage, plus disease as well as additional findings.

It is important to note that zone I disease and posterior zone II disease can progress rapidly and actually skip stages described in the original International Classification [29], meaning that stage 1 (demarcation line) and stage 2 (ridge) can be difficult to identify and classify on ophthalmoscopy (aggressive posterior ROP). An alarming sign in zone I and posterior zone II retinopathy is the formation of pathological vas-

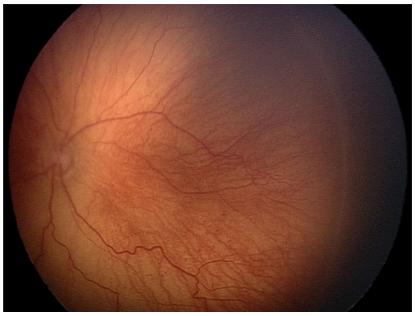


Fig. 5 ▲ Stage 1 ROP in anterior zone II. A *white demarcation line* is visible between the central vascularized and the avascular peripheral retina

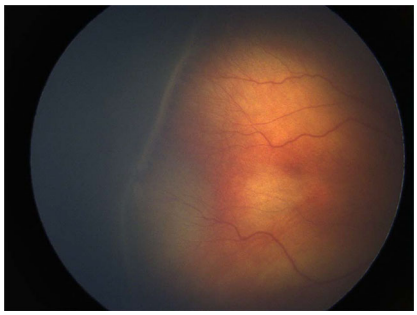


Fig. 6 ▲ Stage 2 ROP. A raised demarcation ridge is visible between the central vascularized and the avascular peripheral retina

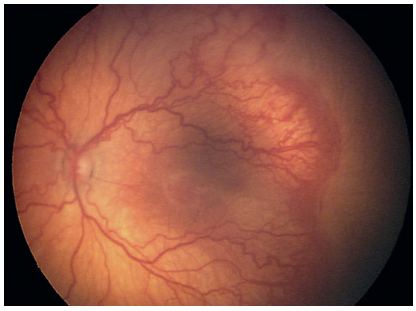


Fig. 7 ▲ Stage 3+ ROP. A raised ridge is visible in posterior zone II between the central vascularized and peripheral avascular retina. Marked proliferations into the vitreous cavity are visible on the ridge. There is also pronounced plus disease, as indicated by vessel tortuosity and dilatation at the posterior pole of the eye

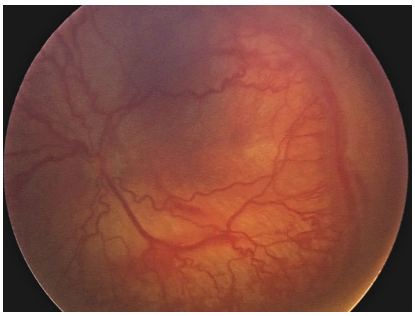


Fig. 8 ▲ Aggressive posterior ROP (AP-ROP) is characterized by rapid progression. The image shows predominantly flat, widely dilated vessels throughout the retinal area. AP-ROP can develop in zone I or central zone II. Urgent treatment is indicated in these cases

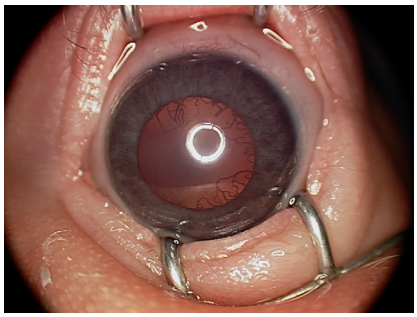


Fig. 9 ▲ Tunica vasculosa lentis. Clearly visible remnants of the tunica vasculosa lentis with dilated vessels and tortuosity can be seen

cular patterns along the border of vascularization.

During the examination, the screening team needs to be aware of the following possible sources of error:

- A regression of findings can be mimicked by transient vasoconstriction (e.g., due to increased arterial partial pressure of oxygen). Furthermore, there is a substantial risk to miss plus disease, if imaging of the retina with a camera is used and the lens is pressed too firmly on the eye.
- Erroneous classification of the extent of retinal vascularization may result from mixing up choroidal and retinal vessels.

Based on the findings of the retinal examination, a subsequent decision shall be made on how to proceed with each individual case, e.g. by:

- Scheduling a follow-up appointment for a repeat ophthalmological examination, or
- Establishing the indication for, scheduling and arranging for treatment, and/or organizing a second-opinion examination by a specialist at a retinology center, along with indicating the level of urgency, or
- Determining that screening can be discontinued if the abovementioned conditions are fulfilled.

All findings, its implications and decisions made shall be documented in a written report. A standardized documentation form shall be used (see example in ◘ **Fig. 2**). ◘ **Figs. 5**, **6**, **7**, **8** **and** **9** show typical findings at various stages of acute ROP.

Ophthalmological follow-up of former preterm infants

Anatomical and functional problems of the eyes occur more frequently in preterm infants as compared to full-term infants. Irrespective of the stage of scarring from ROP, additional changes may occur: refractive anomalies, strabismus, amblyopia, macular hypoplasia, optic nerve atrophy, and cerebral visual impairment. These conditions can permanently impair visual function irrespective of the presence of ROP, or, where applicable, its treatment.

Follow-up eye examinations should be performed in all preterm infants born at a gestational age of $< 31 + 0$ weeks GA or with < 1500 g birth weight irrespective of the presence of acute ROP, as well as in preterm infants born at a gestational age of between $31 + 0$ and $36 + 6$ weeks GA who developed any stage of ROP and in preterm infants with cerebral parenchymal hemorrhage and/or cystic periventricular leukomalacia (minimum requirements):

- At the age of 6 months: optional depending on findings and risk factors
- At the age of 12 months: mandatory
- Every 6 months until 2 years of age
- Annually between the ages of 3 and 6 years
- After 6 years of age: depending on detected pathology/findings that need to be followed

Following laser coagulation or especially after anti-VEGF therapy, examination appointments shall be scheduled at shorter intervals depending on the findings of the individual case.

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Financing the guideline. This guideline has been drawn-up on a purely voluntary basis.

Declarations

Conflict of interest. Potential author conflicts of interest are summarized in table form on a separate form (2010 AWMF form). The disclosed potential conflicts of interest were assessed by the lead guideline coordinator, the members of the author group, and the guideline officer of the GNPI. Some authors have relationships to the pharmaceutical companies that produce drugs for the treatment of retinopathy of prematurity. However, since this guideline relates explicitly to the diagnosis and not to the treatment of retinopathy of prematurity, no relevant conflicts of interest in the sense of personal advantages that could have compromised the authors' impartiality have been expressed. The overview in table form can be viewed on the AWMF homepage: https://www.awmf.org/fileadmin/user_upload/Leitlinien/024_Ges_fuer_Neonatologie_und_Paediatrische_Intensivmedizin/024-010i_S2k_Augenaerztliche_Screening-Untersuchung_Frühgeborene_2020-07.pdf

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case. The supplement containing this article is not sponsored by industry.

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