PROGRESSIVE ROP: ACCEPT OR TAKE ACTION

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ROP DEVELOPMENT

General idea is that

Incidence and severity of ROP is increased by

Extra oxygen

Erytrocyte transfusions

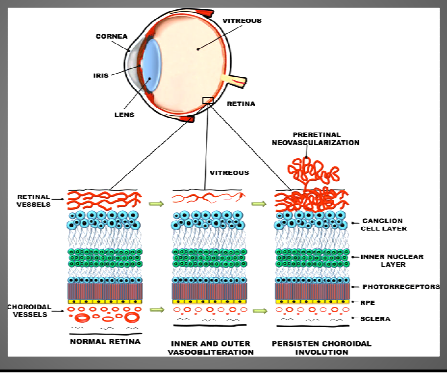
ROP DEVELOPMENT

Retinal changes are always seen at the same moments in time

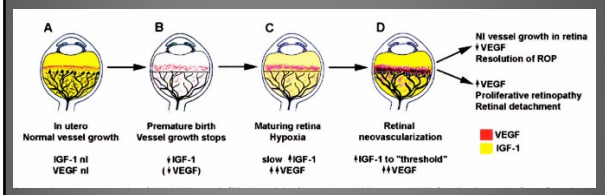
ROP DEVELOPMENT

First signs of ROP	32 wkn PMA
Laser treatment	34-38 wkn PMA
Retinal Detachment	40 wkn PMA

ROP DEVELOPMENT



ROP DEVELOPMENT



PHASE 1 ROP AND O_2

From Birth to 32 wks PMA

Increased SpO2

↓

Hyperoxia

↓

Down regulation of the retinal angiogenesis

PHASE 2 ROP AND O_2

From 33 wks PMA

Decreased SpO_2

↓

Hypoxia

↓

Increase in VEGF levels and low levels of IGF-1

↓

Vasoproliferation

ROP and O_2

ROP AND O_2

SpO_2 in Phase 1 or 2

ROP AND O_2

Phase 1

ROP O_2

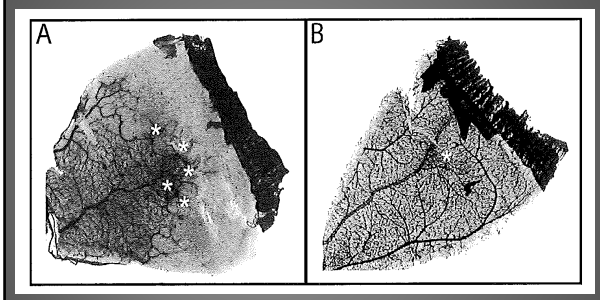
Phase 1 (birth untill 32 wkn PMA)
Vaso-obliterative

First 3 days after birth O2 most effect on the development of ROP

Doublees the chance on Type1/Threshold ROP in zone 1, 70% more chance getting plus signs

Hauspurg, Blood gases and ROP: the ELGAN study, Neonatology, 1104-11:99:2011

ROP O_2



Winners-Mendazibal, Hypoxia-hyperoxia paradigms in the development of ROP of oxygen-induced retinopathy in a rat pup model, J of Neonatol-Perinatol Med 113-7:7:2014

ROP O_2

Level of SpO_2

Recent 3 studies

SUPPORT, COT en BOOST II

Looks at the effect of high (90-95%) and low (85-89%) levels of SpO_2 in Phase 1 (birth-32wks PMA)

Carlo, SUPPORT study group. Target ranges of oxygen saturation in extremely preterm infants, N Engl J Med 1959-69:362:2010
Schmidt, Canadian Oxygen Trail (COT) Group, JAMA 2111-20:309:2013
Darlow, Benefits of oxygensaturation targeting (BOOST), J Pediatr 30-35:165:2014

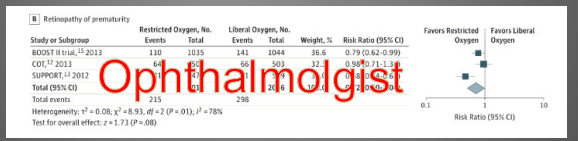
ROP O_2

Neonatologist

Manja, Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis, JAMA pediatrics 332-40:169:2015

ROP O_2

Neonatologist



Ophthalmologist

Manja, Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis, JAMA pediatrics 332-40:169:2015

ROP O_2

Meta-analysis showed that the quality of evidence is low for the estimate of effect of low mortality before discharge with the higher SpO^2 target.

Manja, Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis, JAMA pediatrics 332-40:169:2015

ROP O_2

The lower SpO_2 target group had a tendency toward reduced severe ROP

Manja, Oxygen saturation target range for extremely preterm infants: and outcomes at 18-24month; asysthematic review, Pediatrics 139;:2017

ROP O_2

Maxima Medical Center

Target SpO_2 between 88-95%

Manja, Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis, JAMA pediatrics 332-40:169:2015

ROP O_2

Phase 1

The SpO_2 is dictated by the Neonatal literature at the present moment.

ROP AND O_2

Phase 2

ROP O_2

Phase 2

Retinal hypoxia leading to vasoprolifation

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ROP O_2

Phase 2

Retinal hypoxia leading to vasoprolifation

With adequate oxygenation abnormal vessel growth regresses.

ROP O_2

STOP-ROP study

Objective:
Can higher levels of SpO_2 decrease the progression of ROP and reduce the number of treated eyes.

STOP-ROP, a randomized controlled trail: 1 primary outcomes, Pediatrics 295-310:105:2000

ROP O_2

STOP-ROP study

A trend but a significant decrease in the number of treated eyes in Type 1 ROP except in eyes without plus signs.

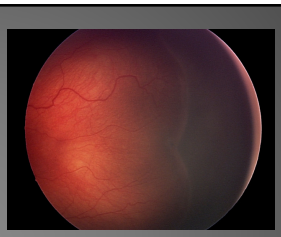
STOP-ROP, a randomized controlled trail: 1 primary outcomes, Pediatrics 295-310:105:2000

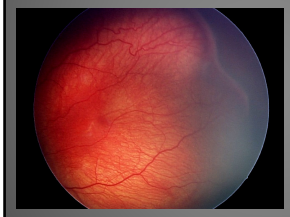
ROP O_2

SpO_2 96-99%
>32 wkn PMA

ROP O_2

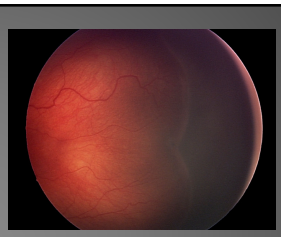
SpO_2 96-99%
>32 wkn PMA

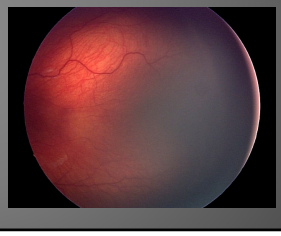


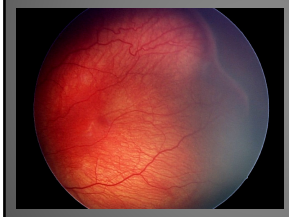


ROP O_2

SpO_2 96-99%
>32 wkn PMA







ROP O_2

Progressive ROP and elevation of SpO_2 (>95%)

Prevention of treatment in progressieve ROP without plus signs

ROP O_2

Progressive ROP and elevation of SpO_2 (>95%)

Prevention of treatment in progressieve ROP without plus signs

Delay of treatment in progressive ROP with plus signs

ROP O_2

Progressive ROP and elevation of SpO_2 (>95%)

Delay of treatment in progressive ROP with plus signs

Transfer for treatment needed
Sick infants
Delay → older children → anesthesia easier

PHASE 2 ROP AND O_2

From 33 wks PMA

Increased SpO_2
↓
Less tissue hypoxia
↓
Decrease in VEGF levels and low levels of IGF-1
↓
Less Vasoproliferation

ROP O_2

Phase 2

The SpO_2 is dictated by the Opthalmologist who can observe the progression of ROP

ROP and Hb

Progressive ROP with low Hb

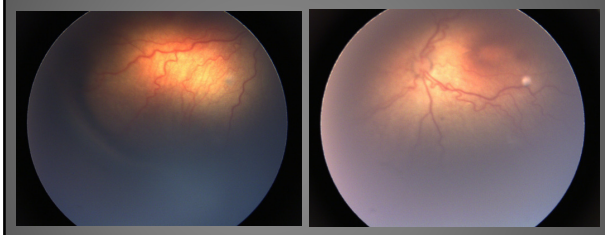
Puck

Gest Age 25^{+1} wks

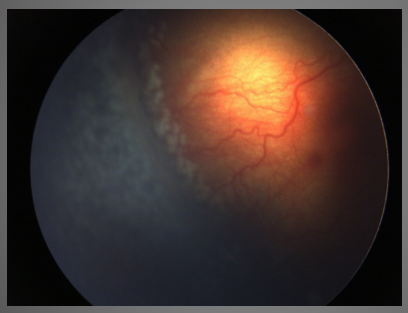
BW 769 gr

ROP 1 in zone 2 for a long period, however in a two weeks window at 41^{+5} severe ROP

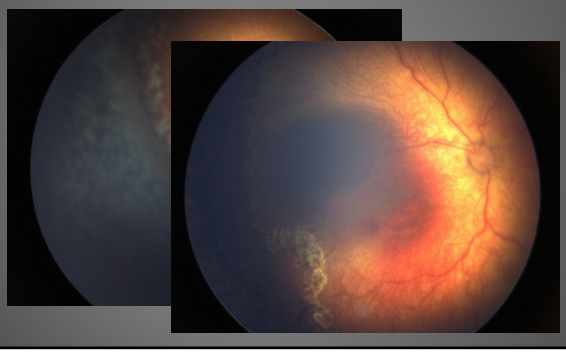
Progressive ROP with low Hb



Progressive ROP with low Hb



Progressive ROP with low Hb



Progressive ROP with low Hb

Puck

- Oxygenation was not changed
- After discharge at the NICU 36 wks PMA
- High care center accepted for weeks a Hb of 5.2-5.4mmol/l and was only treated with ferrofumaraat

ROP AND HB

Englert et al study on Anemia transfusions and ROP

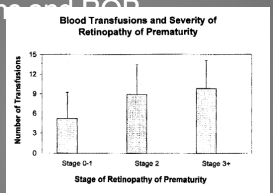


Figure 1. Eighty-seven premature infants with birth weight 508 to 800 g were grouped according to severity of ROP: ≤Stage 1 ($n=25$), stage 2 ($n=41$), and ≥stage 3 (including threshold, $n=25$). Infants with more severe ROP were more likely to have received multiple blood transfusions ($p=0.04$). Error bars represent standard deviation.

Englert et al, Effect of anemia on ROP in extreem low birth weight infants, Journal of Perinatology, 2001;21;121-6

ROP AND HB

Table 2 Infant Characteristics That Potentially Affected the Decision to Transfuse Blood and Their Relationship to Severity of ROP

	≤Stage 1 No. (%) (n = 25)	Stage 2 No. (%) (n = 41)	≥Stage 3 No. (%) (n = 23)	p Value
Bronchopulmonary dysplasia				0.001
present (n = 73)	14 (19)	37 (51)	22 (30)	
absent (n = 14)	9 (64)	4 (29)	1 (7)	
Sepsis				0.46
present (n = 55)	14 (25)	24 (44)	17 (31)	
absent (n = 32)	9 (28)	17 (53)	6 (19)	
Ventilator assistance (days)				0.004
mean ± SD	19.7 ± 17.2	40.9 ± 47.9	37.5 ± 19.5	
median (range)	18 (0–45)	32.5 (0–286)	45 (0–62)	
Supplemental oxygen (days)				0.12
mean ± SD	37.7 ± 30.7	58.4 ± 49.3	58.1 ± 33.0	
median (range)	39 (0–126)	53.5 (0–287)	50 (0–119)	
Length of hospital stay (days)				0.01
mean ± SD	77.7 ± 20.7	104.6 ± 83.4	96.2 ± 24.9	
median (range)	80 (26–121)	89 (11–533)	100 (25–134)	
Total number of transfusions				0.0007
mean ± SD	5.2 ± 4.0	8.9 ± 4.5	9.8 ± 4.2	
median (range)	4 (1–15)	8.5 (0–20)	10 (1–19)	
Number weeks Hct ≤30% or Hgb ≤10 g/dl				0.31
mean ± SD	6.2 ± 2.1	6.3 ± 2.6	7.0 ± 2.6	
median (range)	6 (2–11)	6 (1–12)	7 (1–11)	

Hct, hematocrit; Hgb, hemoglobin.

Englert et al, Effect of anemia on ROP in extreem low birth weight infants, Journal of Perinatology, 2001;21;121-6

ROP AND HB

Table 4 Relationship of Severe Anemia to Highest Stage of ROP Observed

	≤Stage 1	Stage 2	≥Stage 3	p Value (univartate analysis)	p Value (logistic regression)
Number of weeks of severe anemia				0.09	0.03
mean ± SD	2.7 ± 1.7	1.8 ± 1.5	2.3 ± 1.6		
median (range)	3 (0–6)	1 (0–6)	2 (0–6)		
Mean number of transfusions	5.2 ± 4.0	8.9 ± 4.5	9.8 ± 4.2	0.0007	0.12

Severe anemia is defined as hematocrit ≤25% or hemoglobin ≤8 g/dl.

Englert et al, Effect of anemia on ROP in extreem low birth weight infants, Journal of Perinatology, 2001;21;121-6

ROP AND HB

Erdol et al. study on distribution of HbA and HbF in term and premature infants and the effect on ROP

ROP AND HB

Table 2. Hemoglobin (Hb) variant values in babies born at term and premature babies

Hb variant	Term (n = 26)	Premature (n = 49) At birth	Premature (n = 49) At 40 weeks
Weight, g, mean ± SD	3265.7 ± 648.1	1542.8 ± 582.5	3173.0 ± 718.0
HbF, % ± SD	63.83 ± 6.31	70.13 ± 6.06	44.89 ± 13.93
HbA, % ± SD	13.46 ± 4.97	6.39 ± 1.67	34.67 ± 14.23
HbA1b, % ± SD	20.2 ± 5.65	20.11 ± 4.98	10.21 ± 3.87

SD, standard deviation.

Erdol et al, Investegation of the effect of hemoglobin F an A levels on the development of ROP, Journal of AAPOS, 2017;21;136-40

ROP AND HB

Table 4. HbF, HbA, and Hb1Ab values by gestational age in babies with and without ROP

Hb variant	ROP − (n = 23)	ROP + (n = 26)	*P* value
Birth week, mean ± SD	33.04 ± 1.22	29.12 ± 2.39	0.001
Birth weight, g, mean ± SD	1910 ± 560.68	1218.08 ± 375.85	0.001
HbF, % ± SD			
28 weeks	—	71.25 ± 7.01	—
32 weeks	70.98 ± 4.71	50.06 ± 21.49	0.000
36 weeks	61.05 ± 15.37	39.86 ± 21.23	0.001
40 weeks	51.51 ± 12.70	40.70 ± 13.69	0.002
44 weeks	31.24 ± 9.47	37.00 ± 7.99	0.116
HbA, % ± SD			
28 weeks	—	5.76 ± 1.30	—
32 weeks	6.46 ± 1.42	27.86 ± 22.05	0.002
36 weeks	18.16 ± 16.64	38.27 ± 21.89	0.004
40 weeks	29.46 ± 12.39	39.28 ± 14.37	0.009
44 weeks	45.30 ± 13.11	45.02 ± 9.04	0.690
HbA1b, % ± SD			0.783
28 weeks	20.32 ± 4.41	19.89 ± 5.64	
32 weeks	17.39 ± 4.97	14.82 ± 5.41	0.098
36 weeks	14.54 ± 4.56	11.69 ± 5.05	0.066
40 weeks	10.41 ± 4.43	9.93 ± 2.87	0.685
44 weeks	8.57 ± 3.64	7.92 ± 2.34	0.455

SD, standard deviation.

Erdol et al, Investegation of the effect of hemoglobin F an A levels on the development of ROP, Journal of AAPOS, 2017;21;136-40

ROP AND HB

Table 5. Hemoglobin (Hb) levels in babies with and without blood transfusion by month

Hb levels	Babies receiving transfusion = 25	Babies not receiving transfusion n = 24	*P* value
Birth weight, mean ± SD	1244.8 ± 555.2	1853.3 ± 435.1	0.001
Birth week, mean ± SD	29.40 ± 2.71	32.58 ± 1.67	0.001
ROP +, n (%)	20	6	0.001
HbA, % ± SD			
At birth	5.83 ± 1.4	6.98 ± 1.7	0.015
1 month	37.94 ± 19.6	11.96 ± 6.5	0.001
2 months	45.16 ± 16.1	26.11 ± 6.2	0.001
3 months	50.58 ± 11.8	46.87 ± 8.1	0.207
HbF, % ± SD			
At birth	70.03 ± 7.2	70.24 ± 4.7	0.903
1 month	41.48 ± 19.5	66.61 ± 6.6	0.001
2 months	32.88 ± 15.1	53.09 ± 8.1	0.001
3 months	32.18 ± 11.9	36.22 ± 7.2	0.157

ROP, retinopathy of prematurity; *SD*, standard deviation.

Erdol et al, Investegation of the effect of hemoglobin F an A levels on the development of ROP, Journal of AAPOS, 2017;21;136-40

ROP AND HB

Non of these studies made a differentiation in the moment that the anemia is present or the erytrocyte transfusion is given (wks PMA)

PHASE 1 ROP AND HB

From Birth to 32 wks PMA

Transfusion adult blood

↓

Increased HbA

↓

Hyperoxia

↓

Down regulation of the retinal angiogenesis

PHASE 2 ROP AND HB

From 33 wks PMA

Anemia
↓
Less tissue oxygenation
↓
Increase in VEGF
↓
Vasoproliferation

PROGRESSIVE ROP

Something changed in oxygenation ?

Low Hb levels ?

Systemic problems ?

PROGRESSIVE ROP IN THE MMC

Action → Adjust SpO_2 >95%

PROGRESSIVE ROP IN THE MMC

Action → Adjust SpO_2 >95%

Effect → regression of ROP
vessel growth in avasculair zone

(within 10 days)

PROGRESSIVE ROP IN THE MMC

Action ➔ Adjust SpO_2 >95%

Effect ➔ regression of ROP
vessel growth in avasculair zone
(within 10 days)

Action ➔ Check Hb

LASER TREATED ROP

After laser treatment untill first check

LASER TREATED ROP

After laser treatment untill first check

VEGF down regulation take's time after laser

LASER TREATED ROP

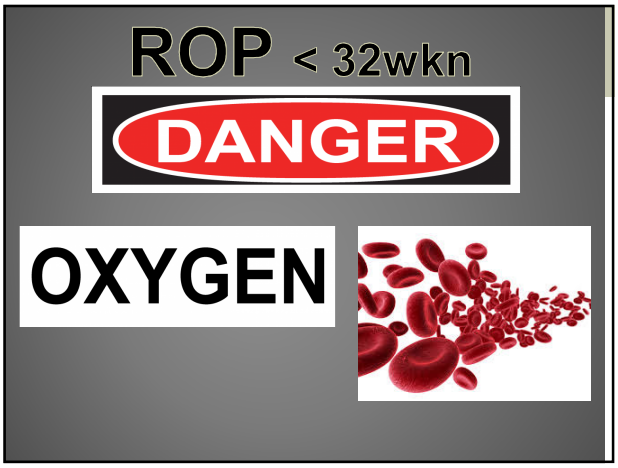
After laser treatment untill first check

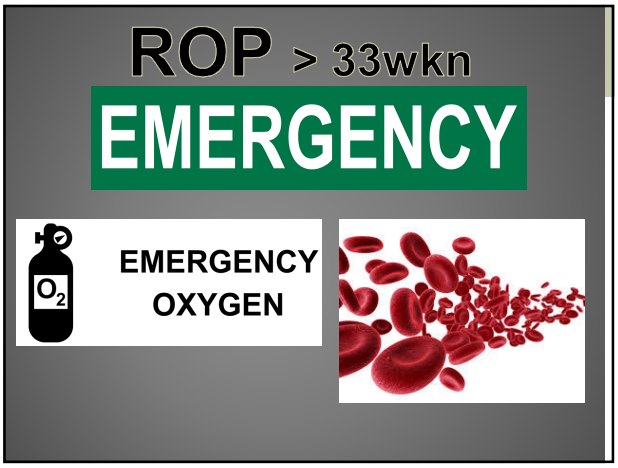
VEGF down regulation take's time after laser

So untill first check after laser:

SpO_2 > 95%

Hb > 7 mmol/l


ROP < 32wkn
DANGER
OXYGEN


ROP > 33wkn
EMERGENCY
EMERGENCY
OXYGEN


Thank you for your
attention