Lower Fetal Hemoglobin Levels at 31- and 34-weeks Post Menstrual Age is Associated with the Development of Retinopathy of Prematurity

PacIFiHER Report No. 1

PacIFiHER Study Group

(**P**reterm **I**nfants and **F**etal **Haemoglobin** in **R**OP)

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Summary

- Fetal hemoglobin (HbF) is the main carrier of oxygen in newborns.
- To date, the temporal relationship between HbF levels and ROP development has not been examined.
- In this prospective cohort study, **low HbF levels** at 31- and 34-weeks post menstrual age (PMA) **increased** the risk of **ROP** by more than seven-fold.
- A **decrease** in HbF **precedes** the **development of ROP** and may play an important role in disease pathogenesis.

Retinopathy of Prematurity (ROP)

https://ualbertaslp.wordpress.com/2014/02/03/the-preterm-infant-ototoxic-drugs-and-the-nicu/

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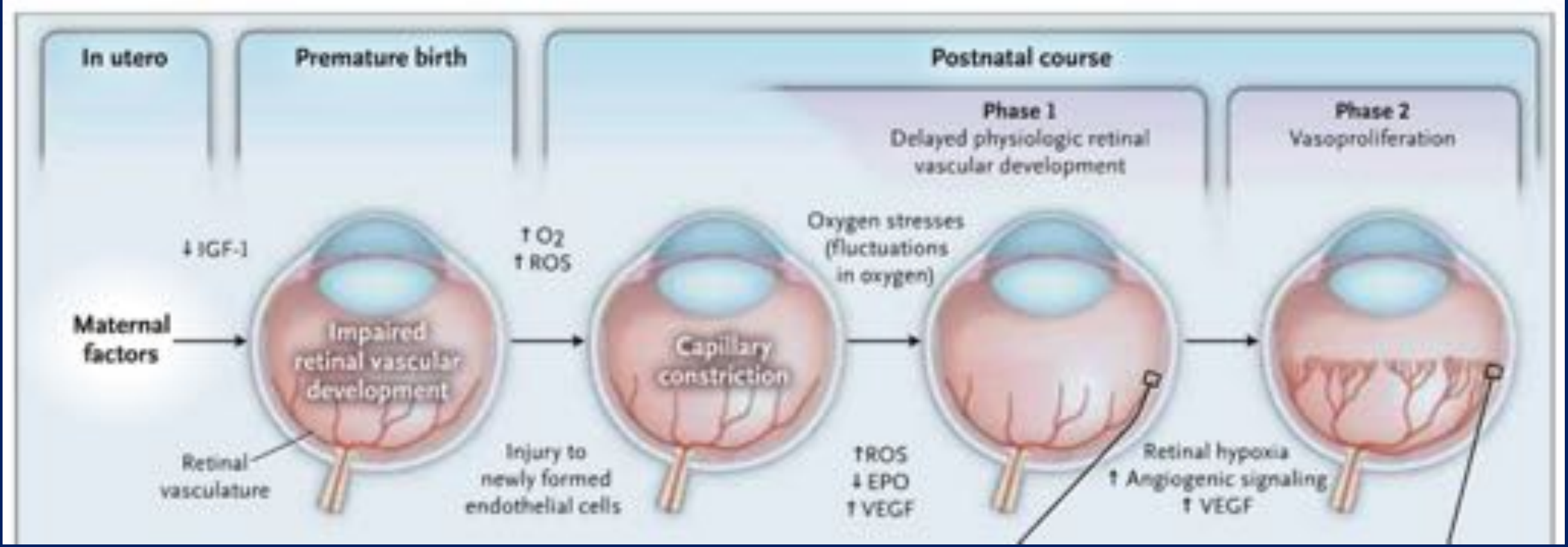
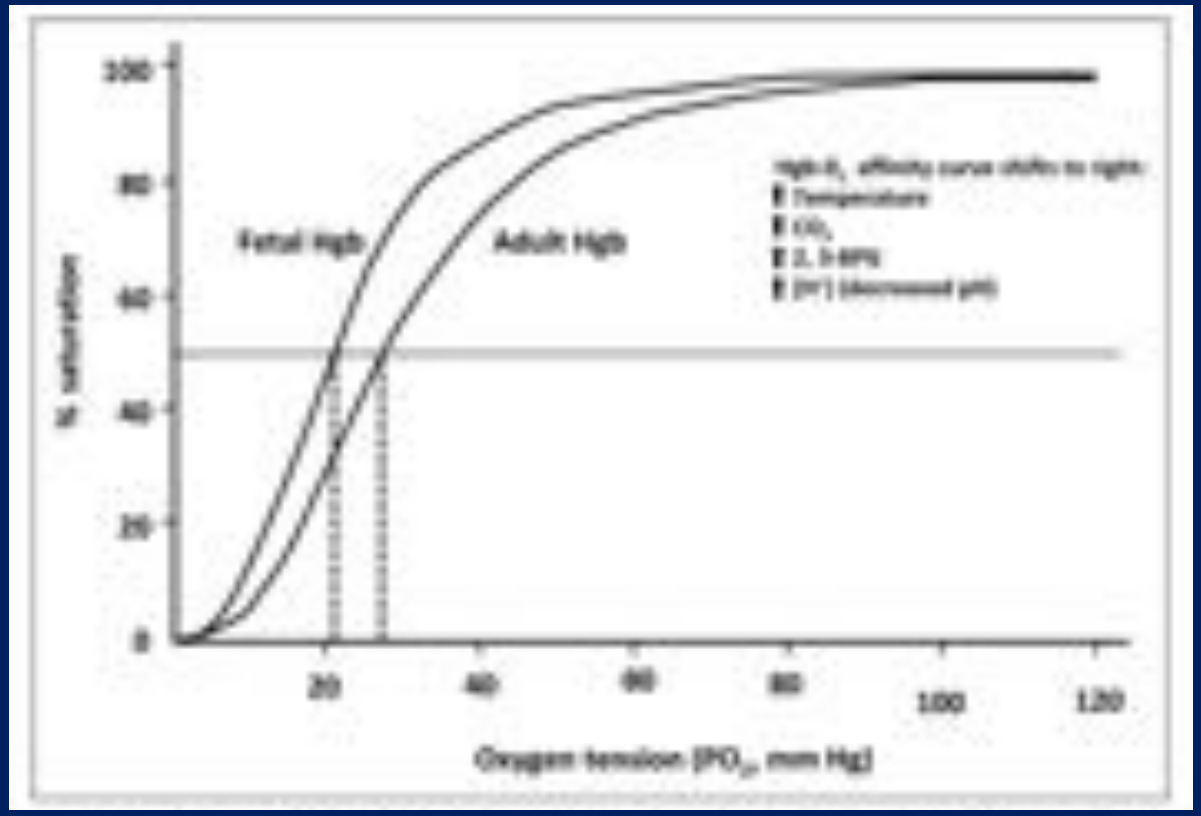
Pathogenesis of ROP



N Engl J Med. 2012 Dec 27; 367(26): 2515–2526.

Fetal vs Adult Hemoglobin

- HbF comprises 90% of total hemoglobin



NeoReviews January 2011, 12 (1) e29-e38

HbF vs HbA

- Increased O_2 affinity
- Left shift oxyhemoglobin curve
- Steeper oxyhemoglobin curve

BETTER O2 deliverer

Prior Studies

- Relationship of HbF levels and risk of ROP development studied in context of blood transfusions with equivocal results
  - Erdol et al – Blood tranfusions with HbA decreased mean HbF levels. **No increased risk of ROP**. [1]
  - Strutchfield et al. Blood transfusions with HbA decreased mean HbF levels. Observed an **increased risk of ROP**.[2]
- Major limitation: temporal relationship between HbF and ROP development not explored.

1. Erdol H et al. Investigation of the effect of hemoglobin F and A levels on development of retinopathy of prematurity. *J AAPOS* 2017; **21**(2)**:** 136-140.

2. Stutchfield et al. Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants: a pilot prospective cohort study. *Eye (Lond)* 2017; **31**(10)**:** 1451-1455.

Study Objective

To characterize the temporal relationship between HbF levels and ROP development.

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Methods

- Single institution prospective cohort study.
- Inclusion: pre-term infants who met the screening criteria for ROP (born < 31 weeks gestational age or <1500 g).
- HbF measured at birth (cord blood), 31-, 34-, and 37-weeks PMA.
- ROP examination performed by expert ROP screeners.

Results

Baseline Patient Characteristics

	No ROP ($n = 45$)	Mild ROP ($n = 12$)	Severe ROP ($n = 3$)	p value
Gender, n(%)				
Male	27 (60)	4 (33)	1 (33)	0.23
Female	18 (40)	8 (67)	2 (67)	
GA (weeks) mean (std); range (weeks)	28.2 (2.0); 24–33	25.5 (1.5); 23–28	23.7 (0.6); 23–26	<0.0001*
Race, n(%)				0.050
Black				
White	20 (44)	3 (25)	0 (0)	
Other	22 (49)	5 (42)	3 (100)	
Multiple Births	3 (7)	4 (33)	0 (0)	0.097
BPD	18 (40)	1 (8)	1 (33)	0.0072*
PD	27 (60)	12 (100)	3 (100)	0.018*
Meningitis	13 (29)	8 (67)	2 (67)	1.0
IVH	3 (7)	0 (0)	0 (0)	0.0097*
Sepsis	11 (24)	8 (67)	2 (67)	0.44
	26 (58)	8 (67)	3 (100)	
Haemoglobin				
(g/dl), birth, mean (std)	16.1 (2.4)	13.5 (1.9)	16.9 (2.8)	0.0084*
Haemoglobin, 31 weeks PMA	13.7 (2.4)	12.4 (2.1)	12.5 (1.1)	0.19
Haemoglobin, 34 weeks PMA	11.8 (4.1)	11.5 (1.5)	11.6 (0.7)	0.98
Haemoglobin, 37 weeks PMA	16.4 (8.9)	13.3 (6.4)	9.7 (1.7)	0.42
BW (g); mean (std); range (g)	1000 (300); 500–1420	800 (200); 420–1220	700 (100); 580–1020	0.018*

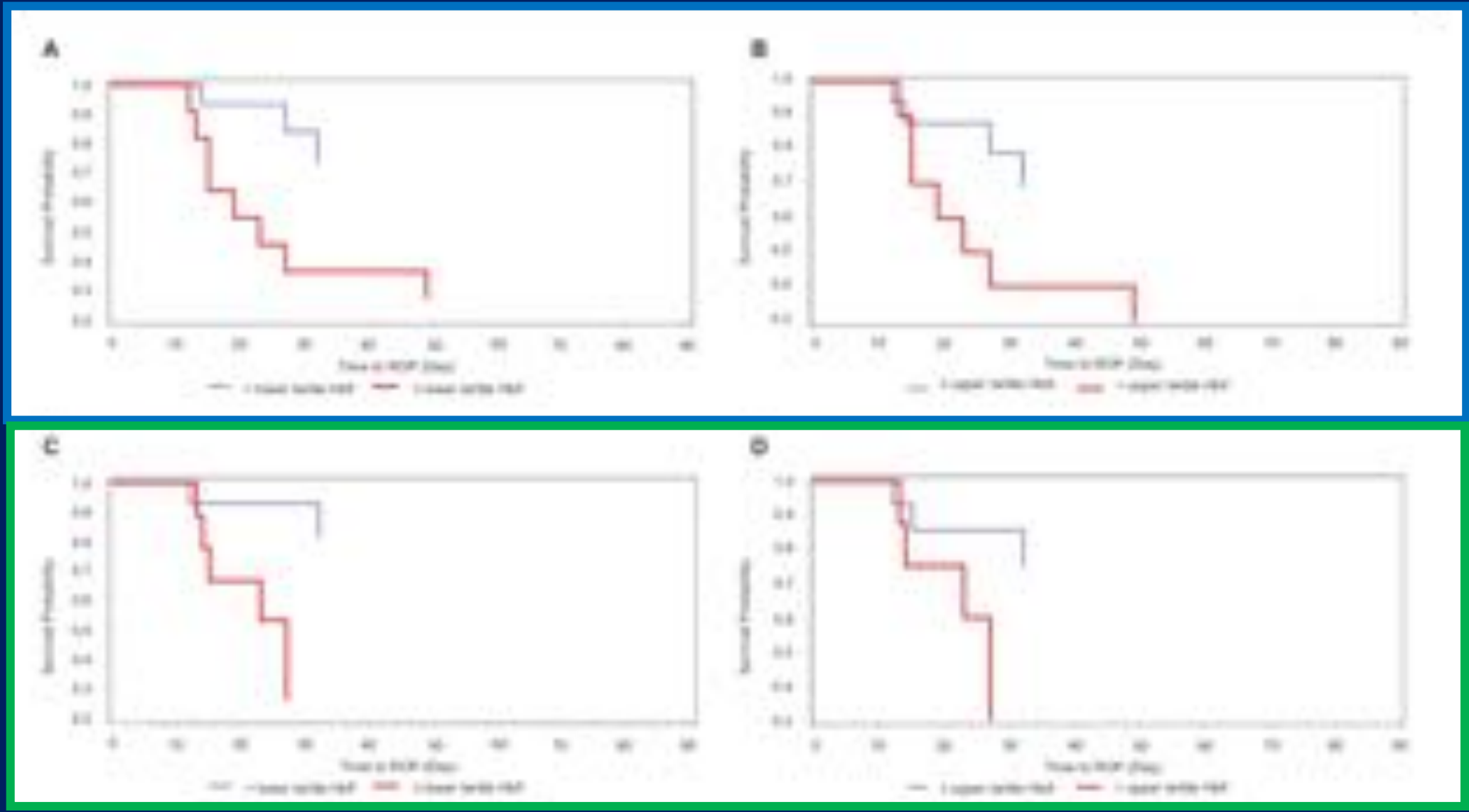
wk week, *std* standard deviation, *GA* gestational age, *BPD* bronchopulomary disease, *PD* patent ductus arteriosus, *IVH* intraventricular haemorrhage, *BW* birthweight, *NA* not available.

*Indicates statistical significance

HbF and HbA levels in preterm infants with and without ROP

	No ROP (n = 45)	Mild ROP (n = 12)	Severe ROP (n = 3)	p value
Cord samples (n)	n = 20	n = 7	n = 0	
Cord HbF, mean (sd)	92.6 (1.3)	93.2 (0.4)	NA	0.24
Cord HbA	7.2 (1.3)	6.8 (0.4)	NA	0.48
Cord HbF/HbA	13.4 (2.5)	13.7 (0.8)	NA	0.70
31 week PMA sample (n)	n = 43	n = 12	n = 3	
HbF, 31 weeks PMA	67.1 (29.6)	28.2 (15.0)	9.7 (2.9)	<0.0001*
HbA, 31 weeks PMA	31.7 (28.5)	69.9 (14.5)	87.7 (2.7)	<0.0001*
HbF/HbA, 31 weeks PMA	7.1 (6.4)	0.5 (0.4)	0.1 (0.04)	0.0009*
34 week PMA sample (n)	n = 35	n = 9	n = 1	
HbF, 34 weeks PMA	60.1 (25.0)	23.3 (14.7)	32.5 (NA)	0.0005*
HbA, 34 weeks PMA	38.4 (24.1)	74.6 (14.2)	66.0 (NA)	0.0004*
HbF/HbA, 34 weeks PMA	3.9 (4.6)	0.4 (0.3)	0.5 (NA)	0.063
37 week PMA sample (n)	n = 21	n = 10	n = 1	
HbF, 37 weeks PMA	60.2 (20.0)	31.9 (15.8)	41.6 (NA)	0.0019*
HbA, 37 weeks PMA	39.1 (19.3)	66.3 (15.3)	57.3 (NA)	0.002*
HbF/HbA, 37 weeks PMA	2.6 (2.5)	0.6 (0.5)	0.7 (NA)	0.051

Kaplan-Meier Curves for ROP Development



31-week PMA

34-week PMA

Cox Proportional Hazard Ratio for Development of ROP based on HbF and HbA levels and PMA

	% total haemoglobin	Hazard ratio (95% CI)	p value
HbF, 31 weeks PMA	HbF ≤ 32.6%	7.6 (2.1–24.0)	0.0006*
HbA, 31 weeks PMA	HbA ≥ 65.7%	5.5 (1.9–16.3)	0.002*
HbF, 34 weeks PMA	HbF ≤ 32.5%	6.3 (2.6–59.0)	0.001*
HbA, 34 weeks PMA	HbA ≥ 66.0 %	7.4 (1.9–29.2)	0.004*

Conclusion:

- Total hemoglobin did not differ amongst infants with and without ROP.
- Low HbF is predictive of ROP development.
- Decrease of fetal hemoglobin levels at 31- and 34-weeks PMA precede onset of clinically evident ROP.
- Future plans to study factors that influence HbF levels and systemic oxygenation.

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