• ROP; Estrés Oxidativo y… ¿Nutrición?

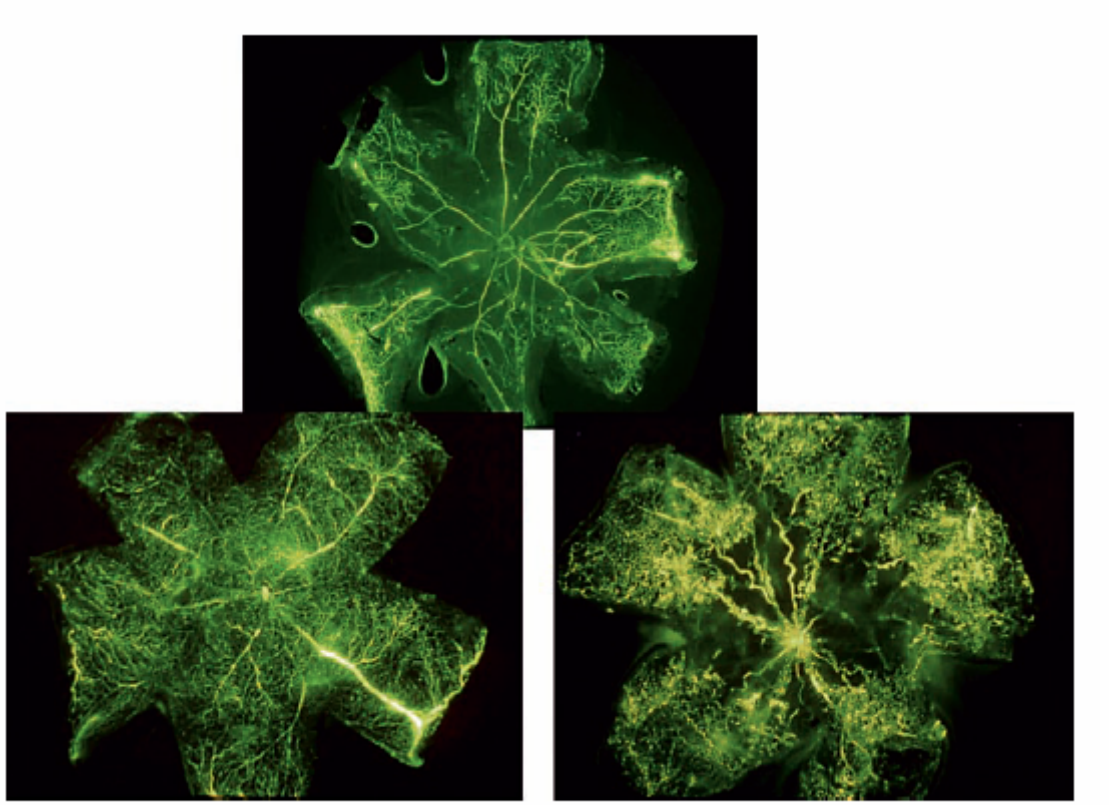
- Alejandro Dinerstein

  Hospital Materno Infantil R. Sardá

  Grupo DE Trabajo Colaborativo Multicéntrico: “Prevención de la Ceguera en la Infancia Por Retinopatía del Prematuro (ROP)

- Buenos Aires septiembre 2010

Retinopatía de la Prematurez



Retinopatía de la Prematuridad

Factores de Riesgo

EG
Oxígeno (hiperoxia/hipoxia)
Estrés Oxidativo
Sepsis
Transfusiones

Nutricionales
BPEG
RCEU
Duración de NPT
Lípidos infundidos
Alteraciones del eje somatotrópico

factores protectores

Crecimiento post natal adecuado
LH?
Lípidos Infundidos
Antioxidantes.

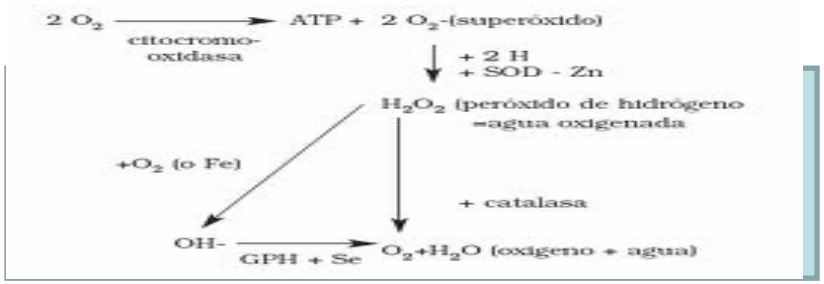
Estrés oxidativo.

Radicales libres

- **Ero**
- **Radicales Superóxido**
- **Peróxido e hidrogeno**
- **Radicales Hidroxilos**
- **Oxigeno sincleto**
- **Peróxidos lipídicos**
- **Carbono**
- **Nitrógeno**
- **Iones Metálicos**

Removedores de Radicales libres

- **Superóxido dismutasa**
- **Catalasas**
- **Peroxidasas**
- **Vitaminas A, C, E**
- **Q10**
- **Ceruloplasmina**



Radicales Libres de Oxigeno

Efectos beneficiosos

- Mecanismos regulatorios
- Información intracelular
- Crecimiento celular
- Diferenciación celular
- Apoptosis
- Respuesta inflamatoria
- Respuesta celular (Sepsis)

Efectos Perniciosos

- Peroxidación de lípidos de Membrana
- Daño oxidativo de proteínas
- Mutación de ADN

Enfermedad por Radicales Libres

DBP

ROP

Injuria Cerebral

NEC

Programación de enfermedades en la vida adulta

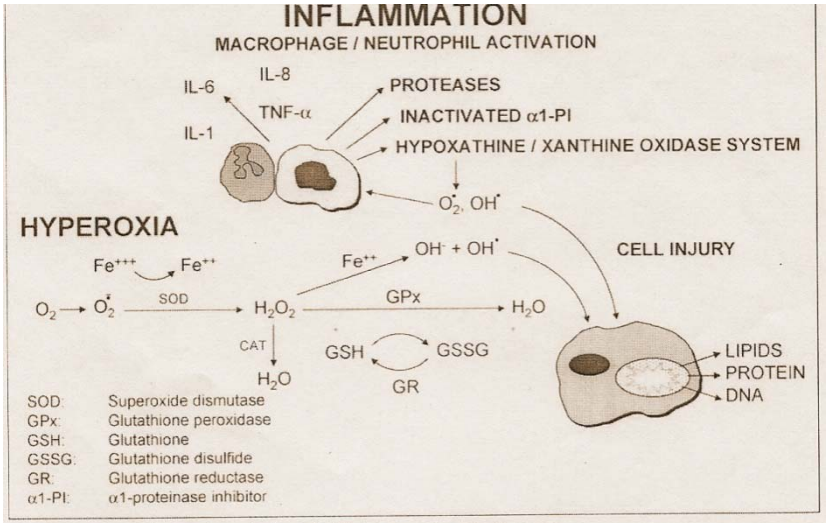


Figure 2. Inflammation/hyperoxia mechanisms of oxidative aggression and cell damage.

Estrés Oxidativo

- **RN Pretérmino**

  Enfermedades Relacionadas con Inmadurez

  Patogénesis: Agresión de los tejidos por ERO Y RL

  Excesiva producción de ERO y Radicales libres

  1- Altas concentraciones de oxigeno durante la reanimación y TTO
  2- Hiperoxia durante la fase de reperfusión
  3- Concentración de Fe libre (transfusiones)
  4- Producción asociada con infección e inflamación
  5- Sepsis
  6- Desnutrición

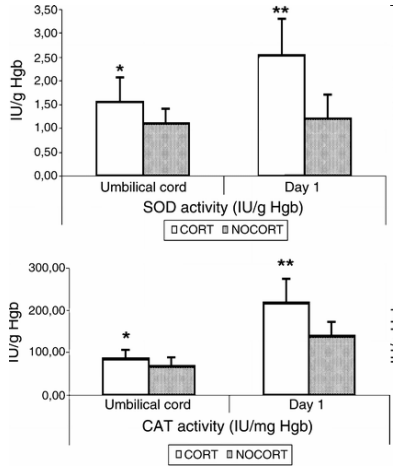
  Disminución de los sistemas enzimáticos y no enzimáticos

ROP Enfermedad producida por Radicales libres

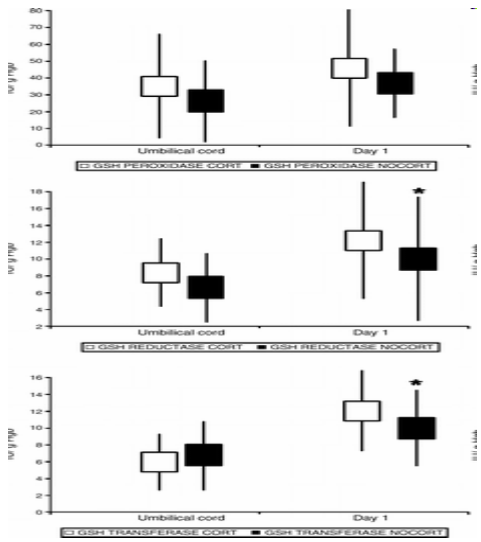
- Mayor incidencia a menor edad gestacional
- Hiperoxia /hipoxia/reperfusión
- Aumento de la Concentración de hipoxantinas (Saugstad 1988)
- Bajo nivel de antioxidantes en la retina.(Chen 1999)
- Efecto protector de D-penicilamina (Lakatos 2006)
- Algún efecto protector de vitamina E (Raju 1997)

Que podemos hacer para disminuir estrés oxidativo?

1- Corticoides prenatales Vento M. Antiox & Redox Sig 2009

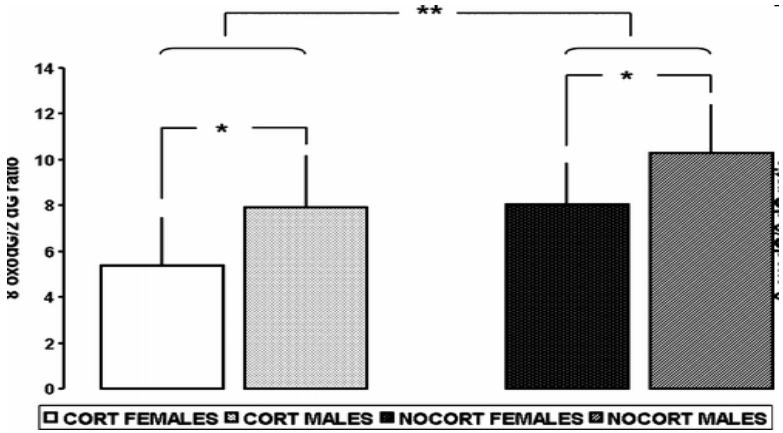


- **Superoxide dismutase (SOD) and catalase (CAT) activities in umbilical cord and day 1 in extremely low gestational-age neonates receiving (CORT group) or not receiving (NOCORT group) a full course of antenatal steroids.**
  Activities are expressed in International Units per gram hemoglobin.



Activities of glutathione redox cycle enzymes (glutathione peroxidase, glutathione reductase, glutathione *S*-transferase) in umbilical cord and at day 1 in BLBW receiving (CORT group) or not receiving (NOCORT group)
Activities are expressed in International Units per gram hemoglobin.

Corticoides prenatales …



- **8-Hydroxy-2'-deoxyguanosine/2'-deoxiguanosine × 100 ratio (8 oxodG/2 dG) in urine collected 24 h after birth in extremely low-gestational-age neonates receiving (CORT group) or not (NOCORT group) a full course of antenatal steroids.** The 8 oxodG/2 dG ratio was significantly higher in patients of the NOCORT group than in those of the CORT group ($p < 0.01$). Within the same study group, male infants excreted significantly ($p < 0.05$) more oxidized bases of DNA than did female infants.

Antenatal Steroids and Antioxidant Enzyme Activity

Vento M Antiox & Redox Sig 2009

Table 2. General Characteristics of Extremely Low-Gestational-Age Neonates (≤28 Week Gestation) Receiving (CORT) or Not (NOCORT) a Full Course of Antenatal Corticosteroids (Betamethasone) According to the Recommendations of the United States National Institutes of Health Consensus Statement (24)

Parameter	*CORT* n=37	*NOCORT* n=20	*Comparison CORT vs. NOCORT*
Gestational age (postconception wk)[a]	27 (24, 28)	27 (24, 28)	NS
Birth weight (g)[b]	786.5± 122.8	755.4±109.3	NS
Gender (m/f)	20/17	12/8	NS
Cord acid/base status[b]	7.12±0.16	7.09±0.12	NS
Apgar 1 min[a]	5 (2, 7)	5 (3, 7)	NS
Apgar 5 min[a]	7 (5, 9)	7 (5, 9)	NS
Type of delivery (vg/cs)	12/25	7/13	NS
Oxygen in the delivery room	78.5%	80.8%	NS
Intubation in the delivery room	55%	58%	NS
Days on oxygen	8 (2, 55)	12 (5, 68)[b]	$p<0.01$
Surfactant-replacement therapy	21 (56.7%)	18 (90.0%)	$p<0.01$
Mechanical ventilation including CPAP (days)	11 (4, 45)	15 (7, 62)	$p<0.01$
Bronchopulmonary dysplasia (BPD)[c]	9 (24.3%)	11 (55%)	$p<0.01$
Patent ductus arteriosus (PAD)	22 (59.5%)	15 (5.0%)	$p<0.01$
Intra-periventricular hemorrhage grades III/IV (IPVH)[c]	8 (21.6%)	11 (55.0%)	$p<0.01$
Retinopathy of prematurity (ROP)[c]	4 (10.8%)	7 (35.0%)	$p<0.05$

[a]Expressed as median CI, 95%.

[b]Expressed as mean±standard deviation.

[c]BPD definition: (33); IPVH grading: (34); ROP grading: (35).

La Reanimación con bajas concentración de oxigeno causa menos Stress Oxidativo, Inflamación y Enfermedad Pulmonar Cronica.

Maximo Vento y col. ***Pediatrics 2009;124;e439-e449***

- **OBJETIVO:**

  Reducir la evolución pulmonar adversa (DBP de 30 a 20%) en RN de 24 a 28 sem.

- **METODO:**

  Se randomizaron a recibir 30% ó 90% de oxígeno durante la reanimación.

  El objetivo de saturación fue de 75 % a los 5 minutos y 85 % a los 10 minutos.

  Se midieron en sangre metabolitos de stress oxidativo.

La Reanimación con bajas concentración de oxigeno causa menos Stress Oxidativo, Inflamación y Enfermedad Pulmonar Cronica.

Maximo Vento y col. ***Pediatrics 2009;124;e439-e449***

RESULTS: The low-oxygen group needed fewer days of oxygen supplementation (6 vs 22 days; $P < .01$) and fewer days of mechanical ventilation (13 vs 27 days; $P < .01$) and had a lower incidence of bronchopulmonary dysplasia at discharge (15.4% vs 31.7%; $P < .05$). GSSG/reduced glutathione × 100 ratios at day 1 and 3 were significantly higher in the high-oxygen group (day 1: high-oxygen group: 13.36 ± 5.25; low-oxygen group: 8.46 ± 3.87; $P < .01$; day 3: high-oxygen group: 8.87 ± 4.40; low-oxygen group: 6.97 ± 3.11; $P < .05$). Urinary markers of oxidative stress were increased significantly in the high-oxygen group, compared with the low-oxygen group, in the first week after birth. GSSG levels on day 3 and urinary isofuran, *o*-tyrosine, and 8-hydroxy-2′-deoxyguanosine levels on day 7 were correlated significantly with development of chronic lung disease.

CONCLUSIONS: Resuscitation of preterm neonates with 30% oxygen causes less oxidative stress, inflammation, need for oxygen, and risk of bronchopulmonary dysplasia. *Pediatrics* 2009;124:e439–e449

Aire ambiental versus oxígeno para la reanimación de neonatos en el momento del nacimiento

- Cochrane 2010

N1 ISSN 1745-9990

- Tan A, Schulze A, O'Donnell CPF, Davis PG

Incidencia de retinopatía del prematuro (RP)
Ningún estudio informa resultados

Que podemos hacer para disminuir estrés oxidativo? Transfusiones y ROP

- Aumento del aporte de oxígeno a la retina
  James L, Eur j Pediatr 1997;156:139-41

  Aumento del Hto

  Hb adulta (afinidad por el oxígeno)
  Cooke R, Eur J Pediatr 1993-152:833-6

- Sobrecarga de Fe

  Menor vida media de los GR transfundidos

  0,5 mg /ml
  Dani C, Arch Dis Child F. N ed, 2003;88:f119-23

- Aumento de hierro libre
- Bajos niveles de ceruloplasmina y transferrina en RNPT
- Lackman , Biol Neonates 1998;74:208-13
- Saturación completa de transferrina
- Simes m; Blood.1974;43:581-90
- Reacción de Fenton
- Producción de radicales libres hidroxilo
- Gutteridge Biochem Soc Trans, 1982;10:72-3

Disminuir el volumen de extracciones

Pensar que respuesta nos ofrece cada determinación de laboratorio. ¿ Que conducta vamos a tomar?

Micrometodos

¿Cuando y como comenzar con el aporte de Fe ?

Que podemos hacer para disminuir estrés oxidativo? Prevenir IIH

- **Sepsis Y Estres Oxidativo**
  Andrades ME. Pediatr Crit care 2009;10(4):467-71

- Lavado de adecuado de manos
- Uso Racional de ATb

Que podemos hacer para disminuir estrés oxidativo? Utilización y monitoreo adecuado del Oxígeno

- Recomendaciones para el control de la saturación de Oxígeno en prematuros

- Comite de Estudios Feto neonatales

  Arch. Argent. Pediatr

  2004;102(4):308-1

- Importancia del uso adecuado del Oxígeno en la UCIN: cuidados respiratorios que previenen la ROP

- Erpen N; Quiropa A.

  Prevención de la ceguera en la infancia por Retinopatia del Prematuro.

  Grupo de trabajo colaborativo multicéntrico: Prevención de la ceguera en la infancia por Retinopatia del Prematuro. UNICEF, MSAL. 2008, Bs As

…y Nutrición?

Duración de NPT.

NPT no protegida de la luz.

Polivitamínicos en NPT

Desnutrición

- Prevención de Estrés oxidativo
- LH ?
- Omega 3/omega 6
- Vitaminas A, E
- Selenio.

LH y ROP

- **Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants.**

Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R. J Perinatol.2001;21(6):349.

RESULTS: Major predictors of ROP were similar in both feeding groups including gestational age, days on mechanical ventilation, and total number of days on supplemental oxygen. The incidence of ROP differed significantly by type of feeding (human milk -41.0% vs. formula -63.5%, p=0.005).

Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.42, 95% CI: 0.19 to 0.93) (p=0.03), controlling for gestational age, duration of supplemental oxygen therapy, 5-minute Apgar score, and race. Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.46, 95% CI: 0.18 to 0.91) (p=0.03), controlling for birthweight, duration of supplemental oxygen therapy, 5-minute Apgar score, and race.

PEDIATRICS Vol. 120 No. 1 July 2007, pp. 1-9 Cherrie D.

Human Milk Intake and Retinopathy of Premature infant in ELBW.

Results: Of the 1057 infants included in this cohort, 788 infants (75%) received at least some Human milk .Among these milk-feed infants the median volume of human milk intake was 30ml/kg/d (interquartile range: 6-83 ml/kg/d) and the median proportional volume of human milk intake was 0.18(interquartile range: 0.03-0.66). One hundred sixty-three infants (15%) developed severe ROP.

Conclusions: In ELBW infants, human milk was not associated with a decreased risk of severe retinopathy of prematurity

Early Hum Dev. 2010 Jun;86(6):391-6. Epub 2010 Jun 18.

The influence of early postnatal nutrition on retinopathy of prematurity in extremely low birth weight infants.

Porcelli PJ, Weaver RG Jr.

Department of Pediatrics, Wake Forest University, Winston-Salem, NC 27157, United States. porcelli@wfubmc.edu

Abstract

BACKGROUND: Retinopathy of prematurity(ROP) is the most common serious ophthalmic disease in preterm infants. Human milk may provide a protective effect for ROP; however, beneficial effects of human milk preclude randomized trials. Therefore, we conducted a retrospective analysis comparing early postnatal nutrition with ROP development.

OBJECTIVE: Evaluate relationship between early postnatal nutriture and ROP surgery.

DESIGN/METHODS: Nutrition data was collected for inborn AGA infants, BW 700-1000 g. ROP surgery was the primary outcome variable. A single pediatric ophthalmologist supervised examinations. All infants received triweekly IM vitamin A as chronic lung disease prophylaxis (Tyson: NEJM, 1999).

RESULTS: BW and gestational age were 867+/-85 g and 26.3+/-1.2 weeks (n=77, mean+/-1SD). ROP surgery infants(n=11) received more parenteral nutrition, 1648 mL, and less human milk, 13.8 mL/kg-day, and vitamin E, 1.4 mg/kg-day, during the second postnatal week. Human milk was a negative predictor for ROP surgery, odds ratio=0.94. Both groups met vitamin A recommendations; however, 74% was administered via IM injections. Neither group met vitamin E recommendations.

CONCLUSIONS: Human milk feeding, parenteral nutrition volume and vitamin E intake were predictors for ROP surgery. IM vitamin A injections provided the majority of vitamin A; vitamin E administration was insufficient. Improving human milk feeding rates and vitamin dosing options may affect ROP surgery rates.

Estrés Oxidativo Y ¿ROP?...

Despite documentation of increased oxygen radicals in animal models and infants with diseases such as ROP or NEC, it has been difficult to correlate the severity of illness with antioxidant capacity (60) or the amount of oxygen radicals produced (5, 14). Interestingly, in a few studies, providing increased antioxidant defenses did not necessarily alleviate disease processes, suggesting more complex etiologies (67, 68).

Redox plays an important role in embryonic, fetal, and neonatal development. Many examples demonstrate that increased oxidative stress may result in abnormal development, but the literature equally demonstrates that obliterating oxidative stress is deleterious to some aspects of development. Additionally, antioxidant therapies have not yet consistently modified the outcome of diseases of oxygen radicals in prematures, suggesting a multifactorial origin. Future studies with combination therapies may be more successful.

Frontiers in bioscience 2009

Rop y Crecimiento

RCIU

Darlow BA. (Pediatrics 2005). PN **Menor a PC 3**

Allegaert K. (JAAPOS 2003). **PN Menor al percentilo 10**

Bardin C.(Pediatrics 1997) **Menores de 27 s y BPEG**

Hellstrom A. (Pediatrics 2003) **EG, PN, IGF1**

Lofqvist C. Arch Ophtalmol 2006
Hellstrom A. Pediatrics 2009
Lofqvist C. Arch Ophtalmol 2009

RCEU

RCEU

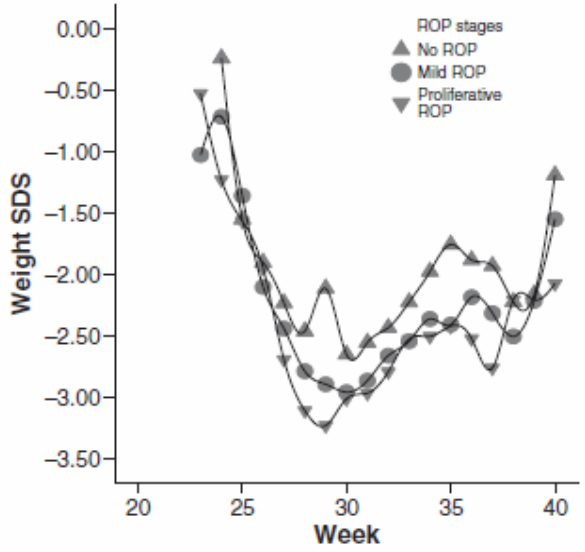


Figure 1 Longitudinal mean weight standard deviation (WSDS) from the historical norm at birth for 131 Swedish infants from week 23 to 40 GA for infants with no ROP (stage 0) (n = 68), mild ROP (stages 1 and 2) (n = 40) and proliferative ROP (stage 3 and above) (n = 23) (10,27).

CONDICIONES CLÍNICAS Y NUTRICIONALES PREDICTORAS DE RETINOPATÍA DE LA PREMATUREZ.

RICARDO M. NIETO Y COL
DIVISION NEONATOLOGIA, MATERNIDAD RAMÓN SARDÁ, BS. AS., ARGENTINA.

SLAIP 2009 / SPR 2010

Condiciones Clínicas y…

ROP	ORa	IC 95 %	Valor de p
Edad gestacional	0.55	0.42 - 0.73	< 0.001
Crecimiento mayor a 20 g/K/día	0.43	0.20 - 0.93	0.031

Calibración del modelo
(acuerdo entre el evento real y predicción del modelo)
Hosmer-Lemeshow chi2(8) = 2.2 Chi^2, p = 0.97

ROP SEVERA Análisis Multivariado

ROP SEVERA	ORa	IC 95 %	Valor de p
Sepsis Tardía	6.8	2.1 - 21	0.001
Crecimiento mayor a 20 g/K/día	0.19	0.050 - 0.75	0.018

…Y Nutrición

- **Crecimiento Post Natal**
- Hellstrom A. 2010
- Porcelli P. 2010
- Hellstrom A. 2009
- Nieto R. 2009
- Lofqvist C. 2006. Crecimiento Post natal y niveles de IGF1

Crecimiento post natal y ROP
¿podemos explicar esta asociación?

- **Concentraciones basales de FCSI 1 se relacionan con la EG**
- **RNPT. Resistencia a HC** Spranger J, Hormone Met Res2000;32 :196-200

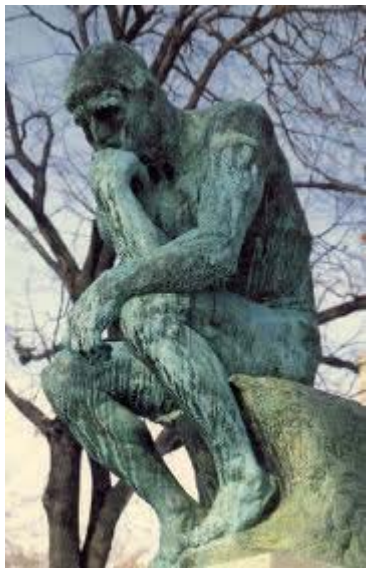
↑ **HC**
⇩ **FCIS 1**

FCEV Mediador de la vascularización

Relación entre niveles de FCIS 1 y FCEV en neovascularización retiniana. (Hellstrom A)

FCSI 1 es necesario para para que el FCEV estimule fosforilación de Akt/PKB

↓ **Concentraciones de FCIS 1 Se asocian con** ↑ROP



Crecimiento post natal y ROP
¿podemos explicar esta asociación?

.Los niveles séricos de FCIS 1 a la misma EGC es significativamente menor en quienes desarrollan ROP.

. El desarrollo de ROP se asocia significativamente con el tiempo con niveles bajos de FCSI 1.

. Los pacientes con concentraciones en niveles superiores tienen un desarrollo vascular normal.

Table I. Relationship between serum IGF-I concentrations and the development of ROP [14].

	Time from birth for serum IGF-I concentration to rise to 30 μg/l	Mean serum IGF-I concentration at 34 wk PCA	Maximum serum IGF-I concentration at 30–35 wk PCA
Infants who developed ROP (stages 2–5) ($n=10$)	58 d (range 29–120)	25 μg/l (range 21–35)	38 μg/l (range 28–54)
Infants who did not develop ROP (stages 0–1) ($n=19$)	19 d (range 1–79)	43 μg/l (range 11–58)	52 μg/l (range 29–90)
p	< 0.001	< 0.01	< 0.04

PCA: postconceptional age.

Table II. Relationship between serum IGF-I concentrations and time taken from birth for serum IGF-I concentration to reach 33μg/l and the development of ROP—data summary extracted from Hellstrom et al. [20].

	No ROP (stage 0) ($n=37$)	Moderate ROP (stages 1 and 2) ($n=34$)	Proliferative ROP (stage 3) ($n=13$)	p^a
Postmenstrual age (PMA), wk (mean±SD)	28±2	26.7±2	25±1	
Birthweight, g (mean±SD)	1207±350	943±278	738±90	
Serum IGF-I at 30–33 wk PMA, μg/l (mean±SEM) (range)	33±1.72 (16–57)	29±1.76 (15–51)	25±2.41 (14–46)	0.023
Time taken from birth to reach serum IGF of 33μg/l, days (mean±SEM) (range)	23±3 (1–47)	44±5 (0–123)	52±7 (1–101)	0.001

[a]Kruskal-Wallis test with application of Bonferroni procedure for multiple comparisons.

Crecimiento Y ROP

- **FCIS 1 se correlaciona con:**
  EPC: (4.03 ± 0.95ug/l)
  Energía: (0.07 ± 0.01ug/l)
  Energía y proteínas (0.36 ± 0.11ug/l)

- **↓ En niños con desnutrición proteica FCIS 1.** Grant 1973, Hintz 1978

- **Cuando el aporte energético es adecuado los aportes de proteínas se correlacionan con ↑ niveles de FCIS 1.** Maiter 1988

43% del riesgo de ROP proliferativa puede ser explicado por menor EG y niveles bajos de FCSI 1 a las 33s EPC

EG es una constante

Podemos actuar sobre las concentraciones plasmáticas de FCIS 1?

Hellestrom A 2003

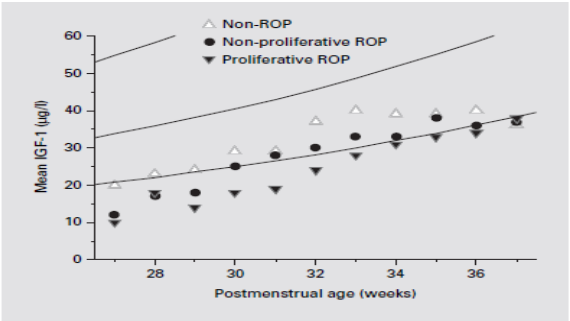


Fig. 4. Longitudinal mean IGF-1 with respect to ROP severity. Mean serum IGF-I values for each postmenstrual week (weeks 29–40) and ROP stages were studied; no ROP (stage 0, n = 37), moderate ROP (stages 1 and 2, n = 34) and proliferative ROP 3 (stage 3, n = 13). The upper, middle and lower red lines depict, respectively, the 95th, median and 5th centile of normal fetal IGF-I levels by using the technique of cordocentesis and an IGF-I assay similar to the one used in the present study [29].

Crecimiento y ROP

RCEU

Comienzos del 3er trimestre el feto recibe entre 3,6 y 4,8 g/k/d de proteínas

Déficits 28 d de vida :

Energía: 732/kcal/k

Proteínas 33/g/kg

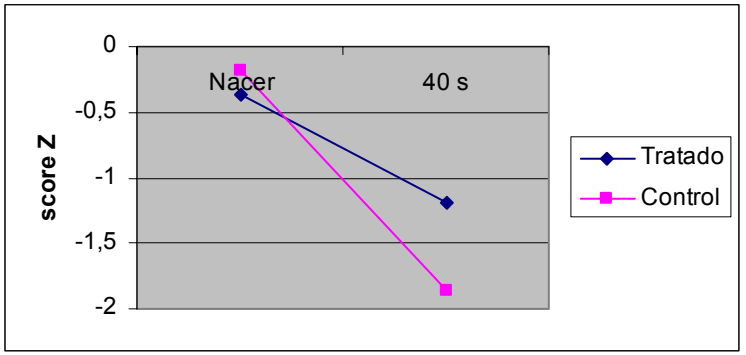
RCEU 73%

Intervención nutricional

Energia 295 Kcal/k

Proteínas 7 g/k

RCEU 56%



- Dinerstein A, Nieto R et al j of perinatol 2006

Crecimiento y ROP Recapitulando…

- **EG**
- **Bajos niveles de FCIS 1**
- **Elevados niveles de HC**

- **Descenso postnatal de los niveles de FCIS1en RNPT**
- **Niveles de FCIS1 se correlacionan directasmente con el aumento de peso y el estado nutricional**

- **Déficit proteico**
- **RCEU**

- **Los niveles de FCSI 1 (evento primario) juegan un rol fundamental en la génesis de ROP.**

- **A mayor RCEU (menores niveles de FCSI 1) mayor incidencia de ROP.**

Tin W 2001

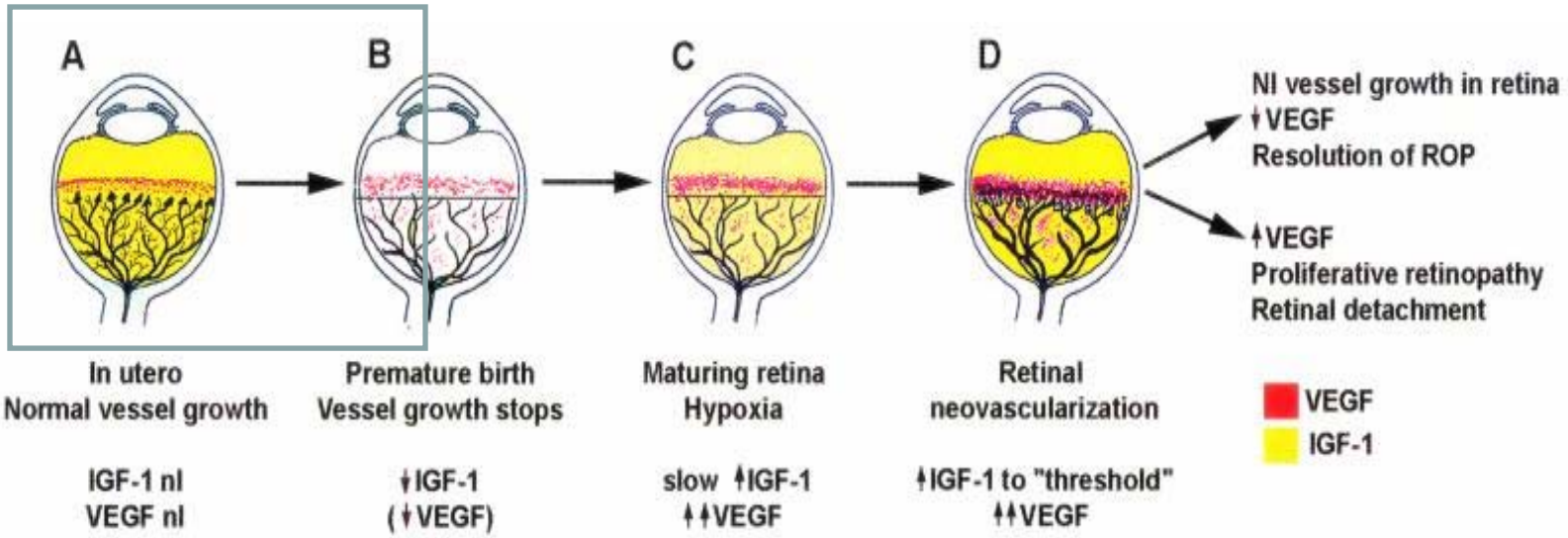
One-year survivors, *n* (%)	One-year survivors with threshold ROP, *n* (%)	Mean ΔSDS weight[a] from birth to discharge	Weight for postconceptional age at <3rd percentile at discharge
65 (52.8%)	18 (27.7%) (95% CI 17–40.2%)	−2.335	29 (45%)

Alternativas???
Intervenciones tendientes a aumentar los niveles de FCIS 1 inmediatamente después del nacimiento

- **No suprimir el aporte de nutrientes enteral y parenteral que recibe el feto IU**

- **NEM con LH**
- **NUTRICIÓN ENTERAL Y PARENTERAL PRECOZ SEGÚN LAS RECOMENDACIONES ACTUALES**

  Evitar déficits proteicos



Para prevenir ROP

- Uso racional de oxígeno.
- Disminuir estrés oxidativo.
- Implementar programas nutricionales que eviten RCEU.

- Gracias

- **Magritte “ El Falso Espejo”**