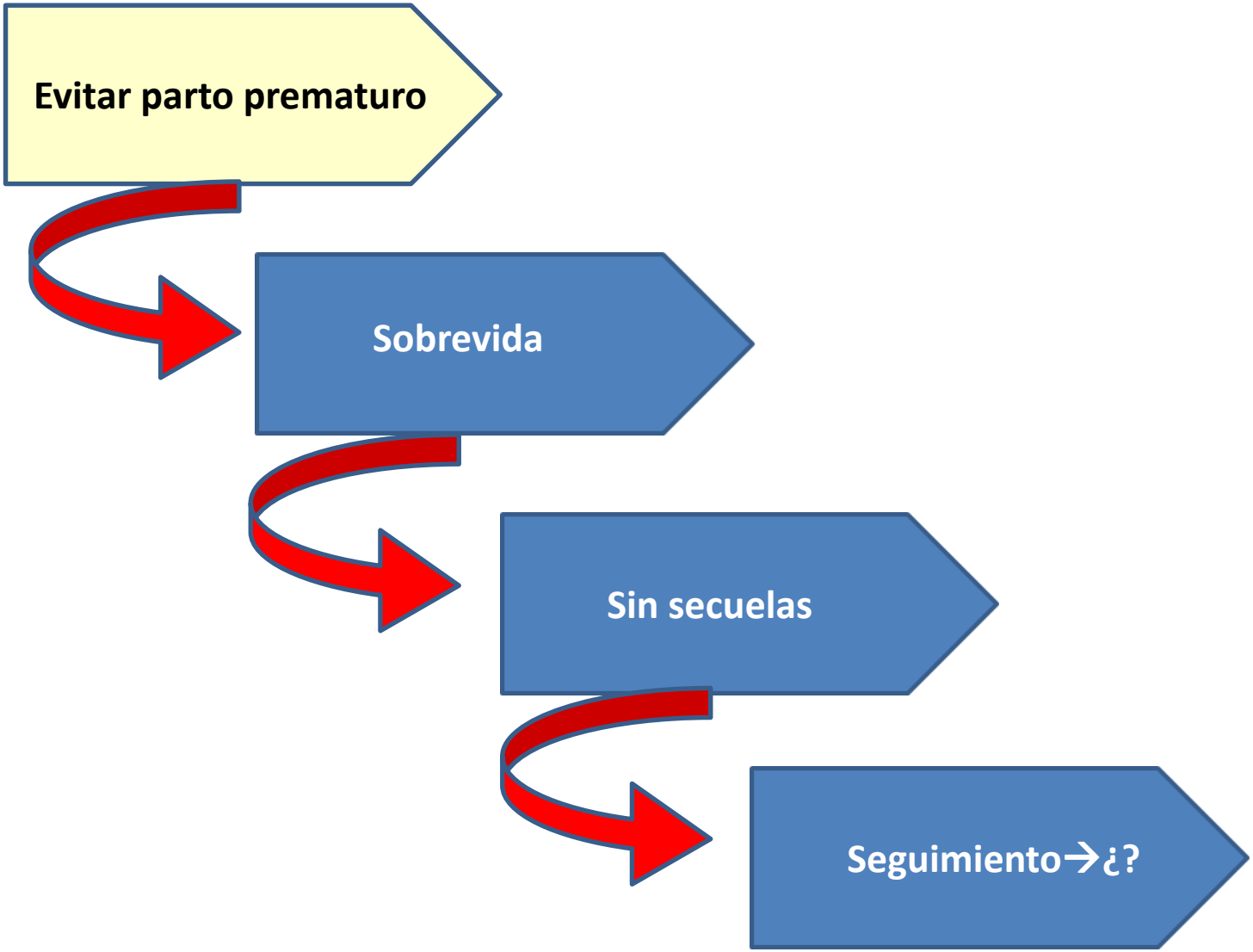
Teaching Course ALANEPE
Septiembre 2019. Valdivia, Chile

Prematurez y Bajo peso de nacimiento: consecuencias renales a futuro

Felipe Cavagnaro
Clínica Alemana de Santiago
Chile

RN Prematuro:
Niveles de acción



En Chile nacen cerca de 18.000 niños prematuros al año

Hechos reales

- 10% de los RN son preT, 1% < 28 sems. EG.*
- La nefrogénesis se completa entre las 34 y 36 semanas de EG. 60% en 3er trimestre (28-34s)
- En niños MBPN nefrogénesis se completa a los 40 días de nacido
- La medicina actual permite la sobrevida de niños nacidos (muy) prematuramente.
- El compromiso multisistémico, incluyendo al renal, es frecuente en estos niños.

Chile

- En nuestro país representan el 7% del total de los nacimientos; un 1% son prematuros extremos -pesan menos de 1.500 g- de los cuales un 75% logra sobrevivir y más de un tercio lo hace con alguna secuela.

Tabla I
NACIMIENTOS PREMATUROS POR CADA 100 NACIMIENTOS

País	% nacimientos prematuros
Costa Rica	13,6
El Salvador	12,8
Honduras	12,2
Belice	10,4
Uruguay	10,1
Nicaragua	9,3
Brasil	9,2
Bolivia	9,0
Colombia	8,8
Panamá	8,1
Venezuela	8,1
Argentina	8,0
Paraguay	7,8
Guatemala	7,7
Perú	7,3
México	7,3
Chile	7,1
Cuba	6,4
Ecuador	5,1

En Chile, en cambio, así como en países desarrollados, los partos prematuros se asocian al aumento de los partos múltiples, la maternidad tardía (en especial después de los 40 años), y la presencia de obesidad, diabetes o hipertensión en la madre.

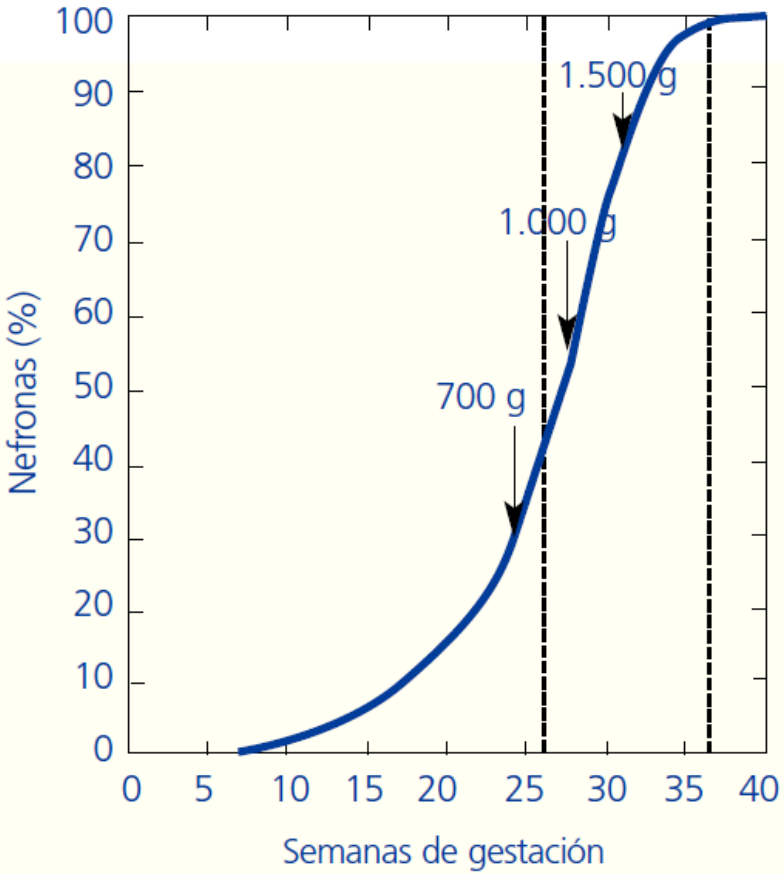
Rev Chil Obstet Ginecol 2016; 81: 330-342

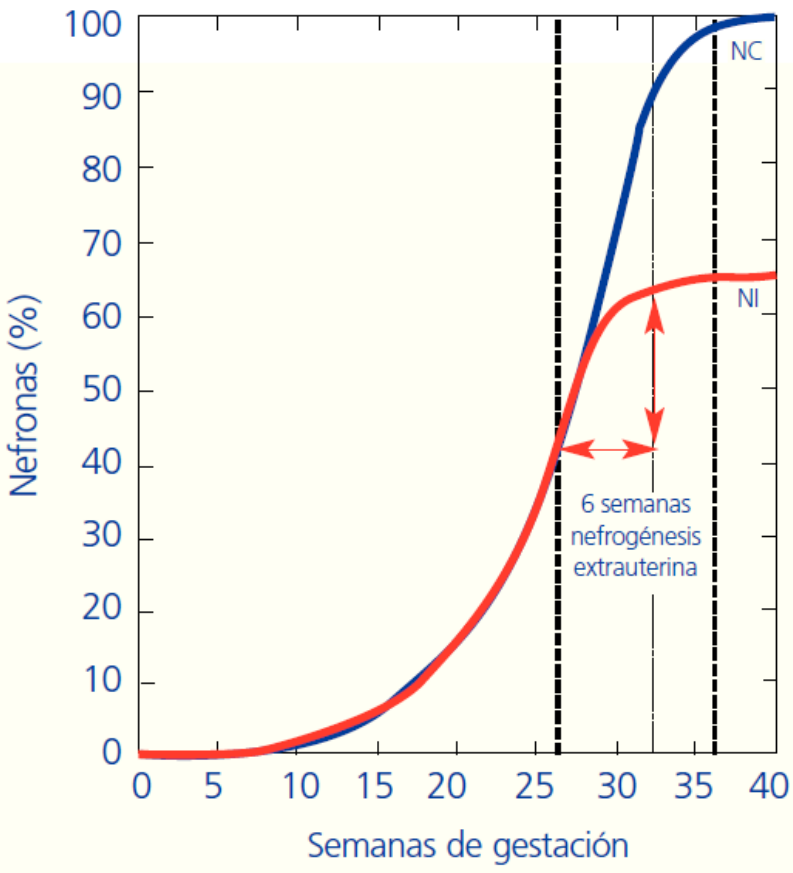
Peso al nacer y su repercusión nefrológica

P.J. Ortega López, I. Zamora Martí
Servicio de Nefrología Pediátrica. Hospital Infantil Universitario La Fe. Valencia

NefroPlus 2011;4(1):1-10
doi:10.3265/NefroPlus.pre2011.Feb.10811

60%





Oligonefropatía neonatal congénita vs. adquirida

Curr Hypertens Rep (2016) 18:28
DOI 10.1007/s11906-016-0637-6

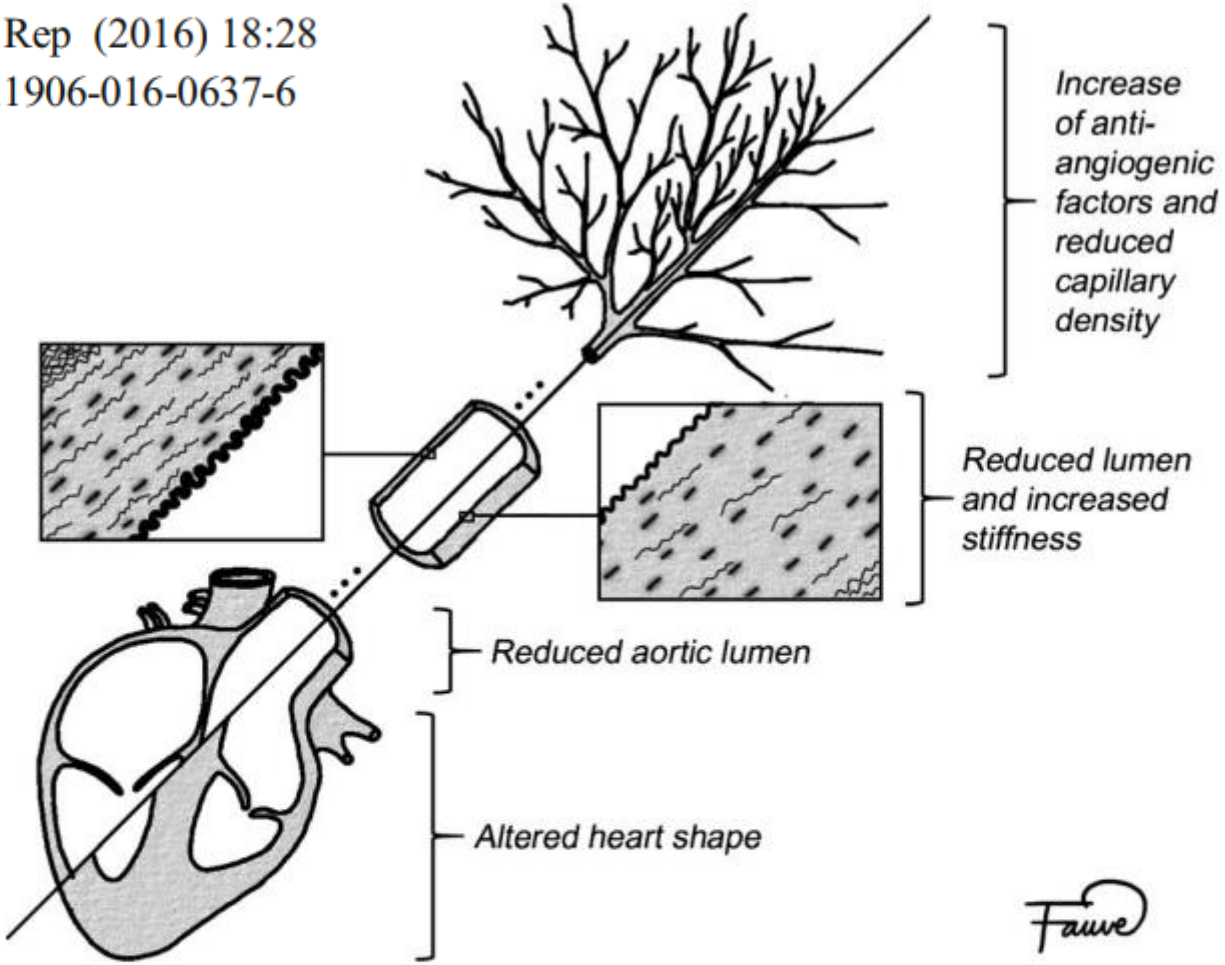
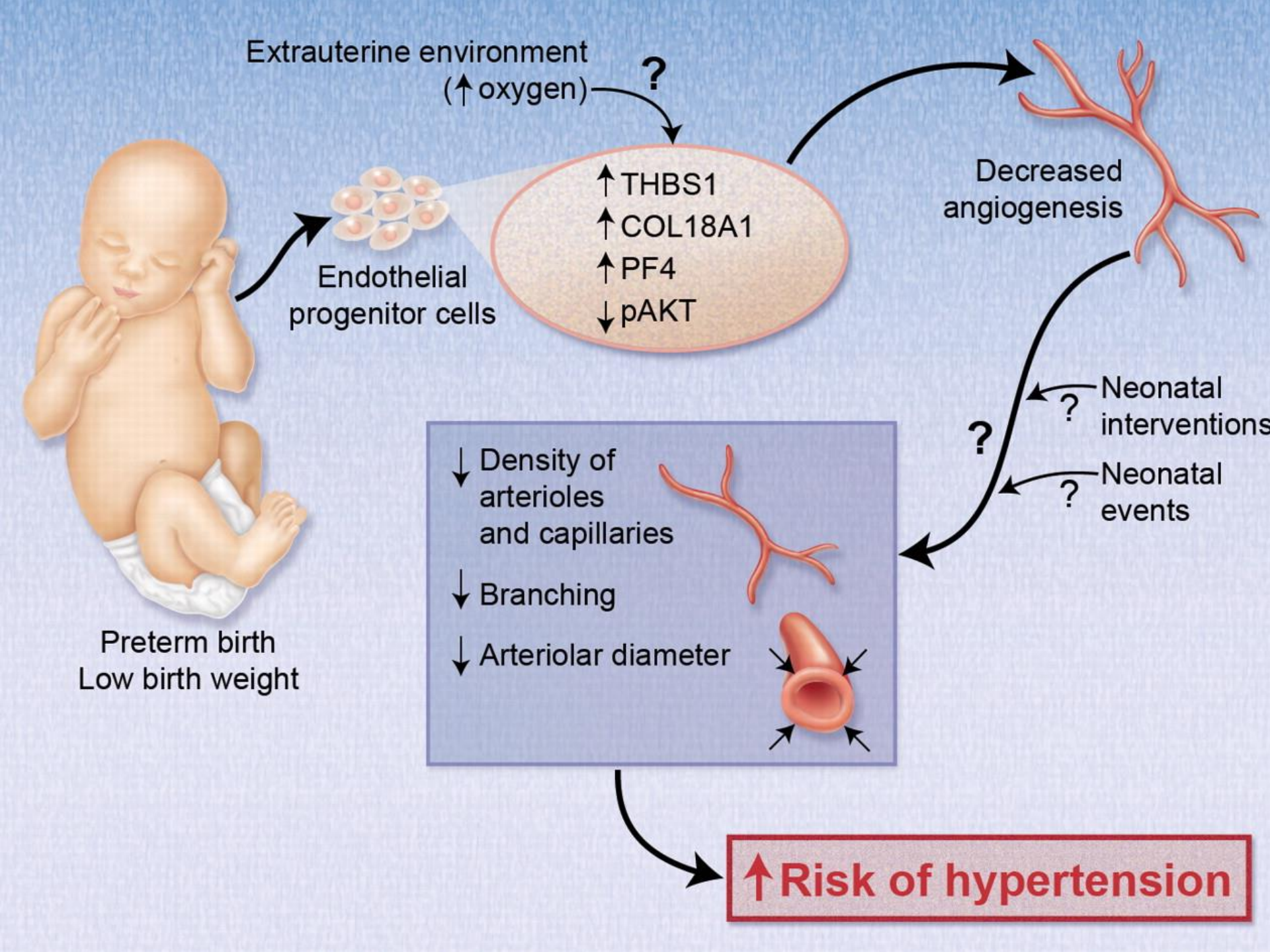


Fig. 1 Schematic representation of changes observed in the cardiovascular system of individuals born preterm as well as experimental animal models of preterm birth-related conditions. Reduced cardiac length with increased ventricle wall thickness, changes in wall structure and stiffness of conduit arteries as well as reduced microvascular density, which associates with an anti-angiogenesis profile, are illustrated and discussed in this review


Extrauterine environment
(↑ oxygen)
?
↑ THBS1
↑ COL18A1
↑ PF4
↓ pAKT
Endothelial progenitor cells
Decreased angiogenesis
Preterm birth
Low birth weight
? Neonatal interventions
? Neonatal events
↓ Density of arterioles and capillaries
↓ Branching
↓ Arteriolar diameter
↑ Risk of hypertension

Blood Pressure in Young Adults Born at Very Low Birth Weight

Adults Born Preterm International Collaboration

Katl
APIC Ad

0–887.

Por cada ↓ 2 mmHg, ↓ 7-14 % riesgo de IAM y ↓ 9-19 % AVE

Table 1
ELBW (

d in

Blood				
Systol				
	Women	4.7 (3.2 to 6.3)†	4.9 (3.0 to 6.8)†	5.3 (3.2 to 7.4)†
Diastolic	All	2.1 (1.3 to 3.0)†	2.4 (1.3 to 3.4)†	2.3 (1.1 to 3.4)†
	Men	1.9 (0.7 to 3.0)†	2.1 (0.6 to 3.5)†	2.0 (0.4 to 3.6)†
	Women	2.4 (1.3 to 3.6)†	2.6 (1.2 to 4.0)†	2.6 (1.0 to 4.3)†

Adjusted for age and cohort (dummy coded). Analyses including both sexes are in addition adjusted by sex. POPS indicates The Dutch Project on Preterm and Small for Gestational Age Infants; and VLBW, very low birth weight.

*In this comparison, cohorts 7 (Vancouver) and 8 (McMaster) include no VLBW subjects so their controls are excluded as well. Cohort 5 (POPS) not included.

†Statistical significance.

Pediatric Nephrology
https://doi.org/10.1007/s00467-018-4050-z

ORIGINAL ARTICLE

Renal function and blood pressure are altered in adolescents born preterm

Andrew M. South[1,2,3] · Patricia A. Nixon[1,4] · Mark C. Chappell[2,5] · Debra I. Diz[2,5] · Gregory B. Russell[6] · Elizabeth T. Jensen[3] · Hossam A. Shaltout[2,7,8] · T. Michael O'Shea[9] · Lisa K. Washburn[1,2]

Received: 27 March 2018 / Revised: 27 July 2018 / Accepted: 7 August 2018

96 RN MBPN vs. 43 RNT, evaluados a los 14 años

Table 2 Blood pressure and renal function in adolescents born preterm compared to those born term

	Preterm $n = 96$	Term $n = 43$
SBP (mmHg)	108.4 (10.0)*	103.8 (6.8)
DBP (mmHg)	62.0 (8.9)*	58.6 (7.9)
SBP z-score	− 0.09 (0.91)*	− 0.67 (0.64)
DBP z-score	− 0.2 (0.83)*	− 0.62 (0.72)
High BP	14 (15%)*	1 (2%)
Elevated BP	10 (10%)	1 (2%)
Stage 1 hypertension	3 (3%)	0 (0%)
Stage 2 hypertension	1 (1%)	0 (0%)
Blood urea nitrogen (mg/dL)	11.7 (3.2)	11.9 (3.1)
Creatinine (mg/dL)	0.8 (0.13)	0.79 (0.11)
eGFR (mL/min/1.73 m^2)	126.2 (21.9)*	134.3 (21.4)
ACR (mg/g)	4.9 [3.0, 11.0]	4.0 [2.5, 10.9]
Albuminuria (ACR > 30 mg/g)	7 (7%)	3 (7%)

Rev Chil Pediatr. 2018;89(1):18-23
DOI: 10.4067/S0370-41062018000100018

ARTÍCULO ORIGINAL

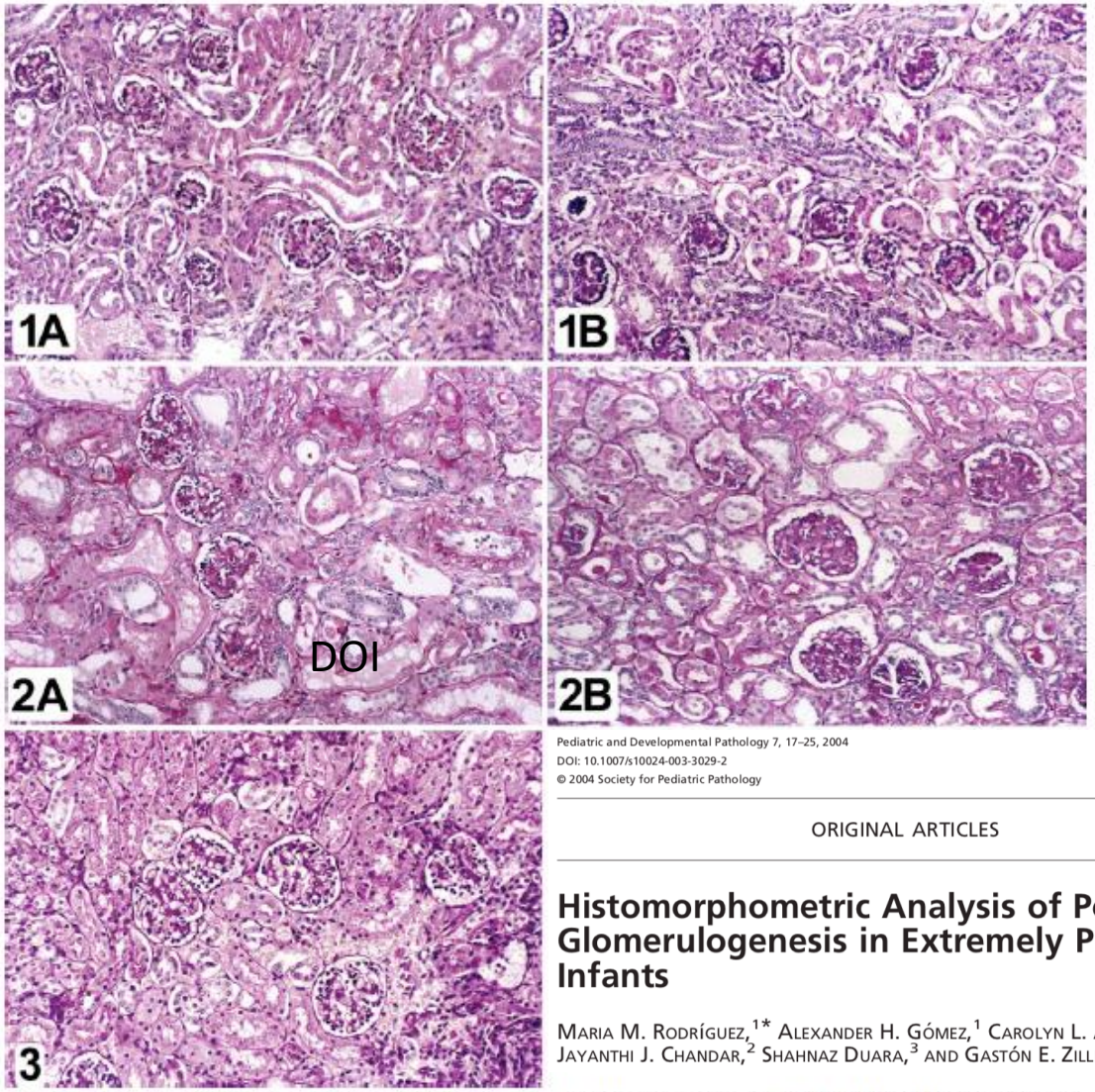
Monitorización ambulatoria de presión arterial en escolares con antecedente de prematurez extrema

Ambulatory blood pressure monitoring in school children with a history of extreme prematurity

Andrea Solís[a], Jaime Cerda[b], Claudia González[c]

19 niños 5-7 años EG 28-31 sems (1000-1556 gr)
11 (58%) con catéter umbilical

9 (47,4%) ausencia de DIP nocturno sistólico y/o diastólico
3 con sospecha de HTA, los 3 obesos
FX renal normal, sin MAU



Pediatric and Developmental Pathology 7, 17–25, 2004
DOI: 10.1007/s10024-003-3029-2

ORIGINAL ARTICLES

Histomorphometric Analysis of Postnatal Glomerulogenesis in Extremely Preterm Infants

Maria M. Rodríguez,[1*] Alexander H. Gómez,[1] Carolyn L. Abitbol,[2] Jayanthi J. Chandar,[2] Shahnaz Duara,[3] and Gastón E. Zilleruelo[2]

Figure 2 Composite photomicrograph depicts examples of each group as studied by computer-assisted morphometry with periodic acid-Schiff-stained slides (20× lens). Groups **1A** and **1B** were very similar regarding glomerular size. However, glomeruli from the group of preterm infants without renal failure (RF) who survived ≥40 days **(2B)** were larger than the preterm group with RF surviving ≥40 days **(2A)** and term infants without RF **(3)**.

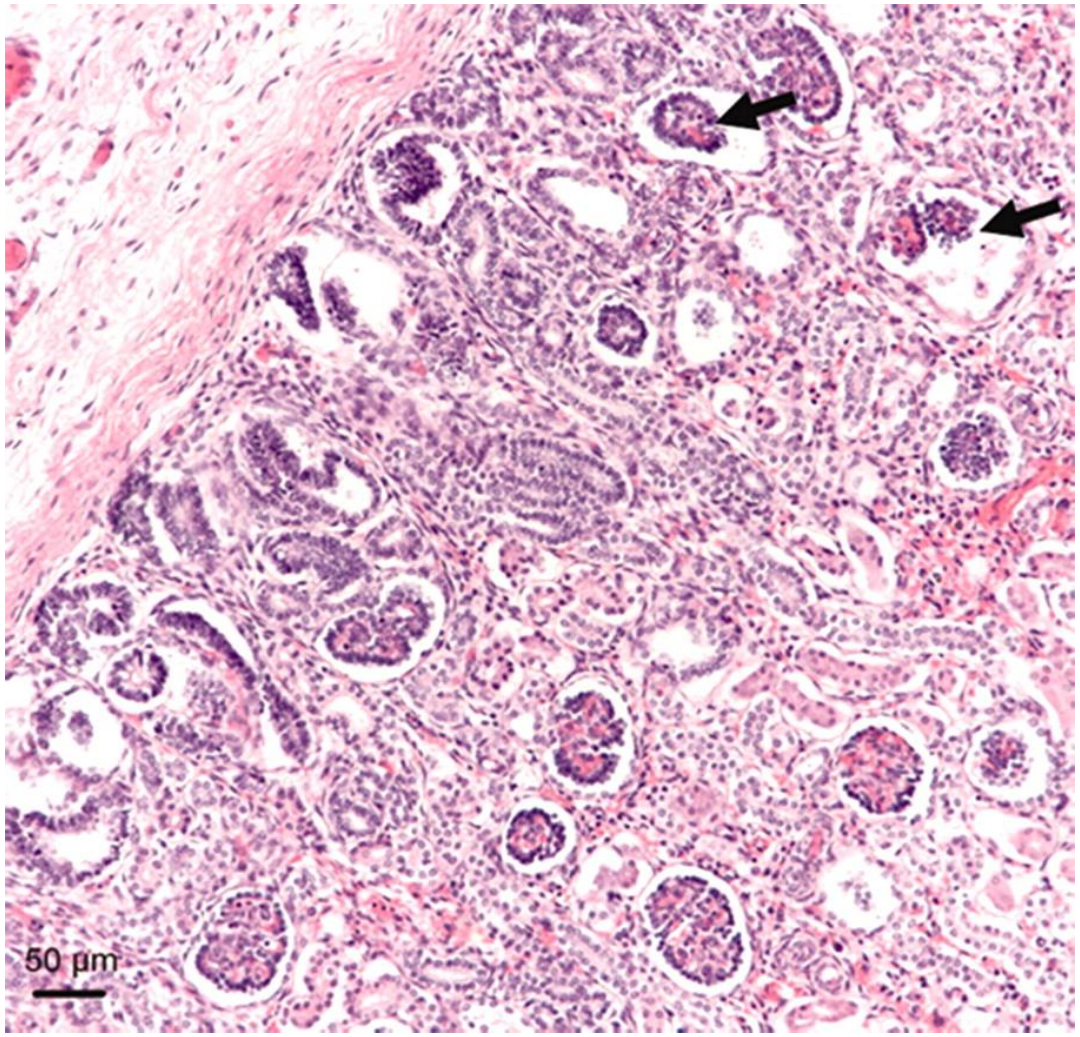
Table 2 Computer-assisted morphometry by groups[a]

	Patient groups (N)				
	Preterm < 40 days		Preterm ≥ 40 days		Term
Variable	1A (16) (RF)	1B (17) (no-RF)	2A (11) (RF)	2B (12) (no-RF)	3 (10) (controls)
Kidney weight (g)	9 ± 4[b]	7 ± 4[b]	56 ± 57	55 ± 37	27 ± 5
RGC (generations)	6.2 ± 0.4	5.6 ± 0.5	6.5 ± 0.7	8.0 ± 1.2[c]	10.4 ± 0.8[d]
BCA (μm^2)	6413 ± 897	6289 ± 923	8835 ± 2558	9852 ± 3546[e]	6596 ± 721
MTA (μm^2)	3904 ± 547	4350 ± 682	5549 ± 1824	6862 ± 2712[e]	4469 ± 369

RGC, radial glomerular count; BCA, Bowman capsule area, MTA, mesangial tuft area.
[a]Fifty glomeruli were analyzed per patient. Values are means ± standard deviations.
[b]Significantly different from groups 2A, 2B; $P < 0.001$.
[c]Significantly different from other preterm (groups 1A, 1B, 2A); $P < 0.001$.
[d]Significantly different from all other groups; $P < 0.001$.
[e]Significantly different from short survivors (groups 1A, 1B, 3); $P < 0.01$.

Rodríguez M. Ped Dev Pathol 2004

Abnormal glomerular morphology in the kidney of a preterm neonate.



Megan R. Sutherland et al. JASN 2011;22:1365-1374

JASN Journal of the American Society of Nephrology

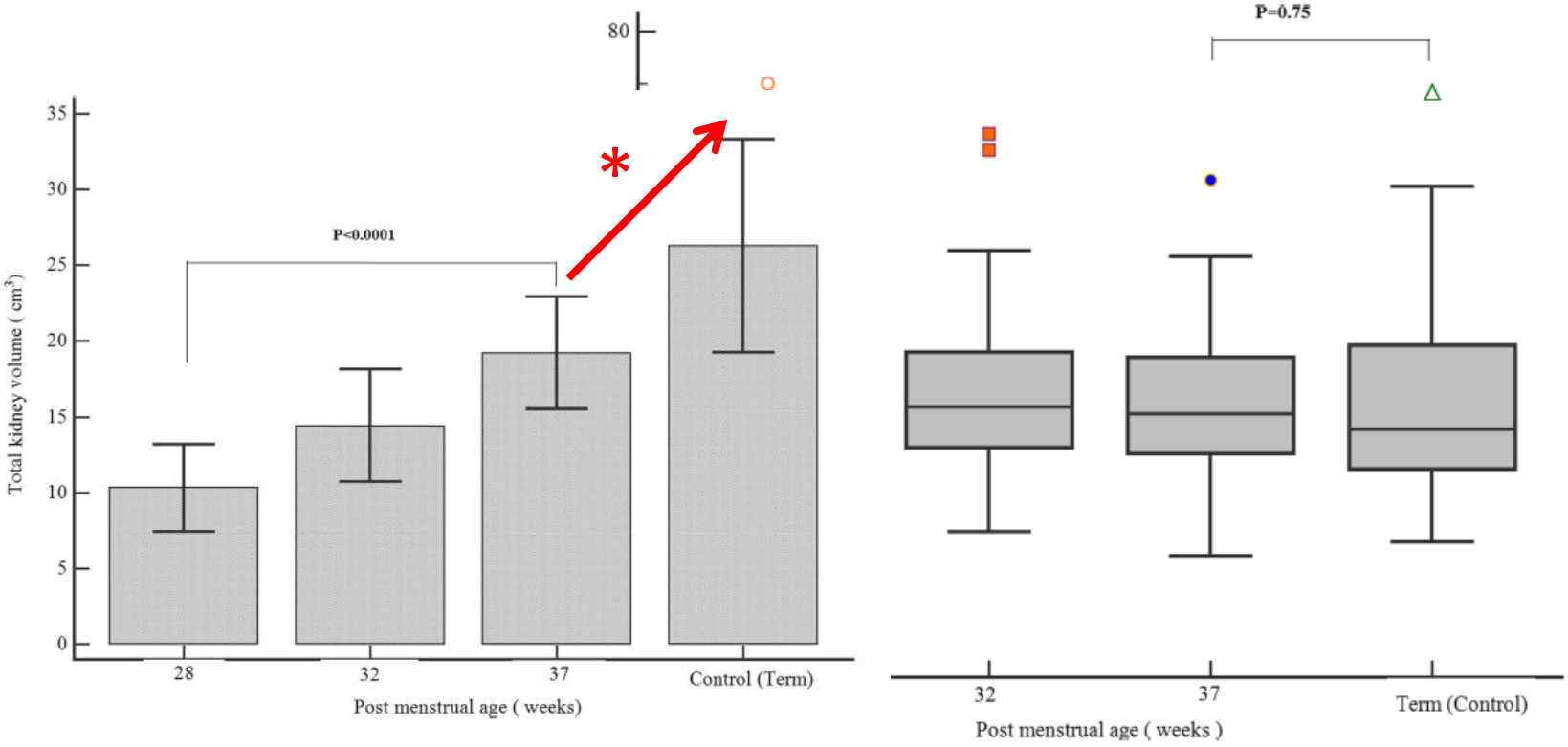
Pediatric Nephrology (2018) 33:1007–1012
https://doi.org/10.1007/s00467-018-3899-1

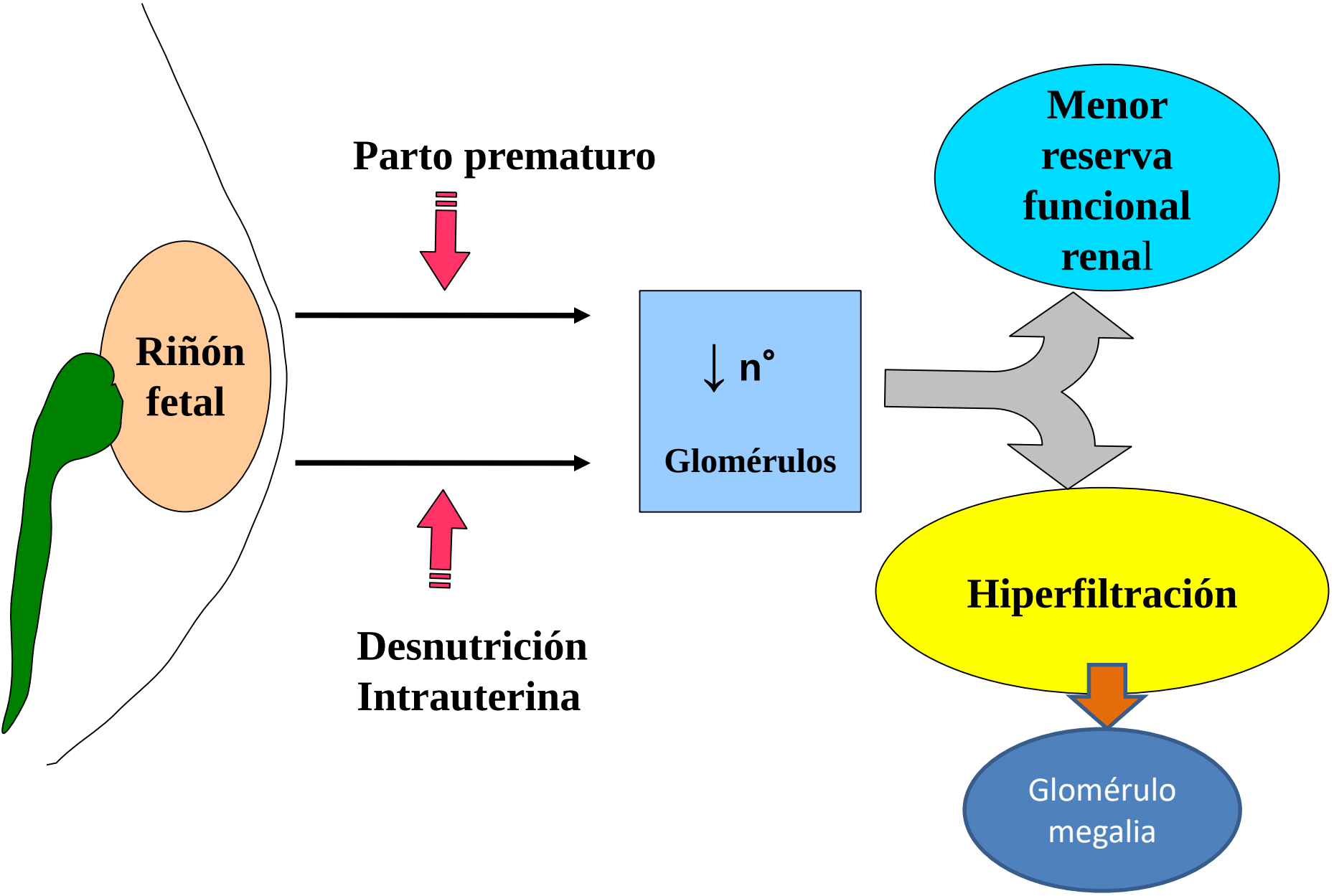
ORIGINAL ARTICLE

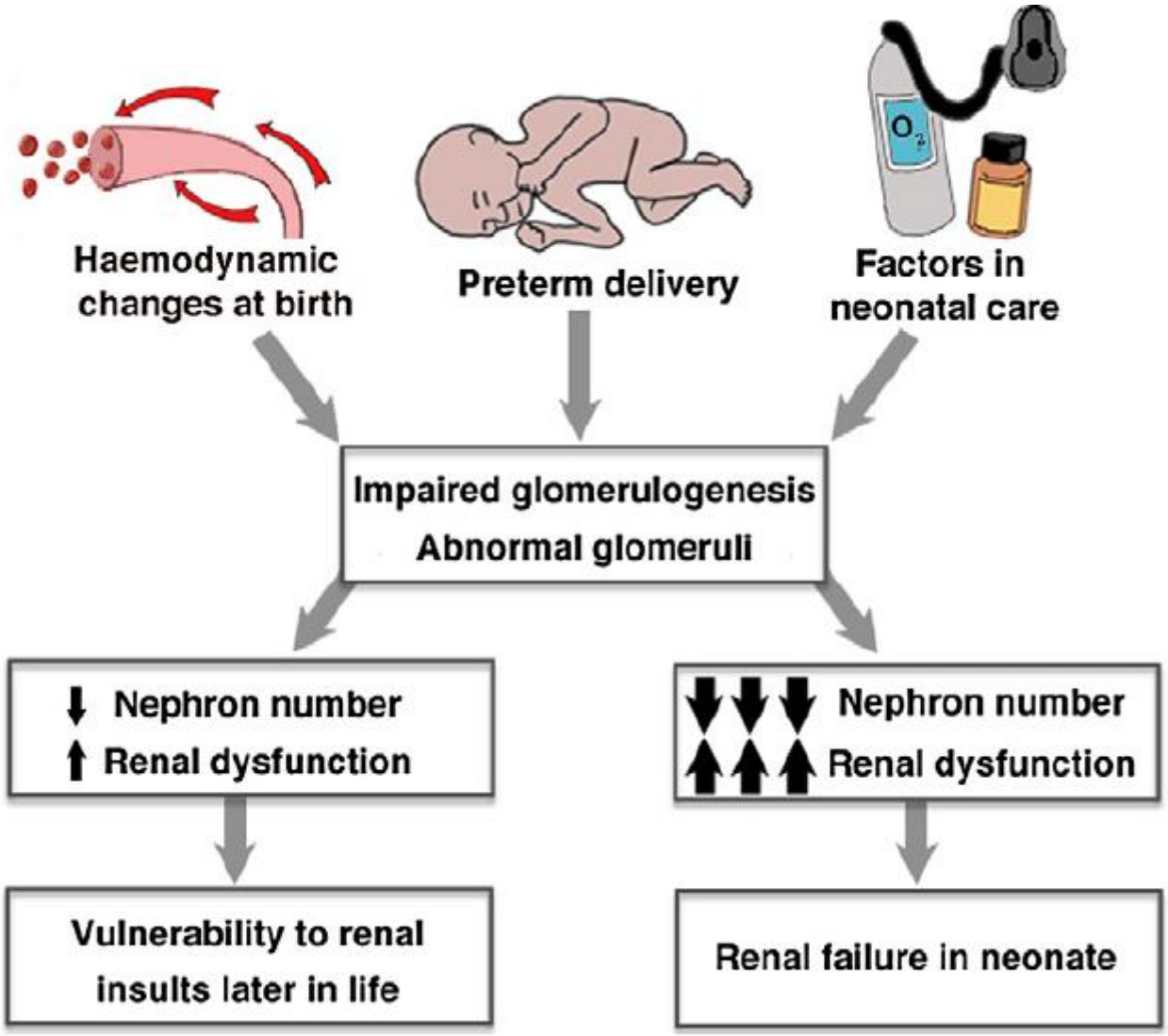
Extra uterine development of preterm kidneys

Yogavijayan Kandasamy[1,2,3] · Donna Rudd[3] · Roger Smith[2] · Eugenie R Lumbers[2,4] · Ian MR Wright[2,5]

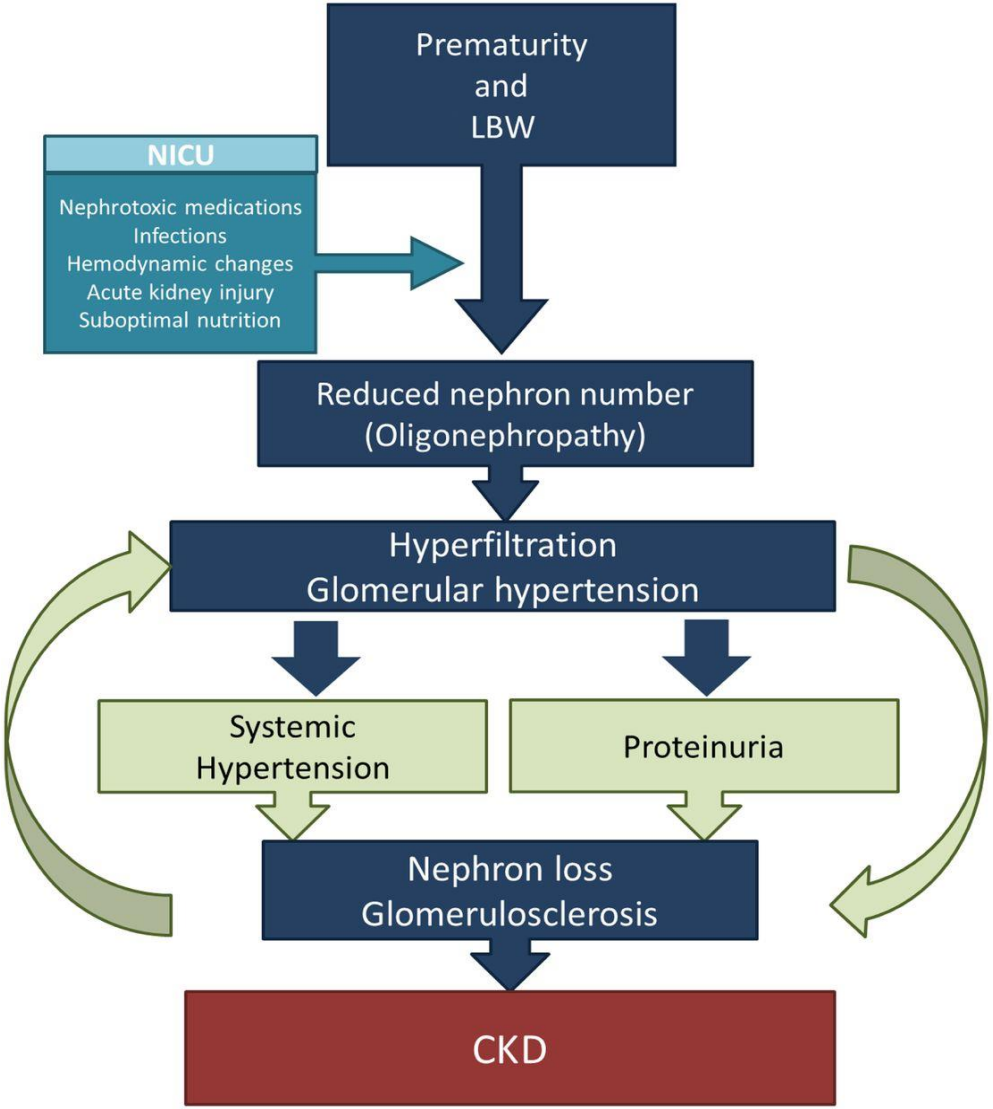
54 preT 26 sems. EG vs. 31 T 39 sems. EG



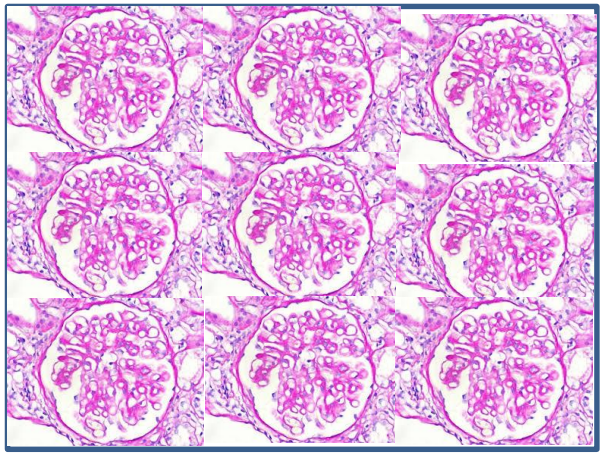

Parto prematuro
Riñón fetal
↓ n°
Glomérulos
Menor reserva funcional renal
Hiperfiltración
Desnutrición Intrauterina
Glomérulo megalia


Haemodynamic changes at birth
Preterm delivery
Factors in neonatal care
Impaired glomerulogenesis
Abnormal glomeruli
Nephron number
Renal dysfunction
Vulnerability to renal insults later in life
Nephron number
Renal dysfunction
Renal failure in neonate

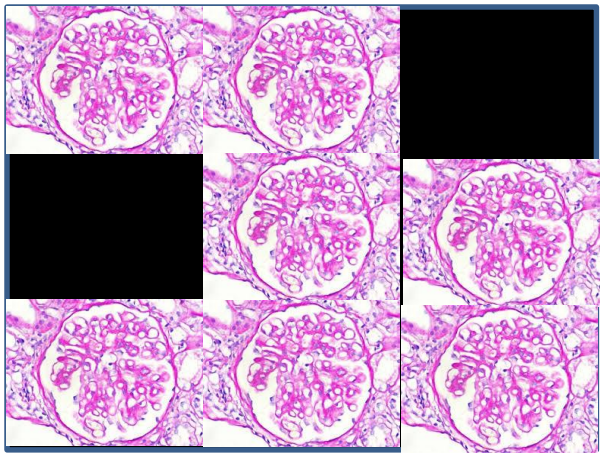
According to Brenner's hypothesis, reduced nephron number (oligonephropathy) leads to hyperfiltration, hypertension, and proteinuria, which perpetuate renal damage and lead to glomerulosclerosis and CKD.16,150 Infants born prematurely have additional risk f...

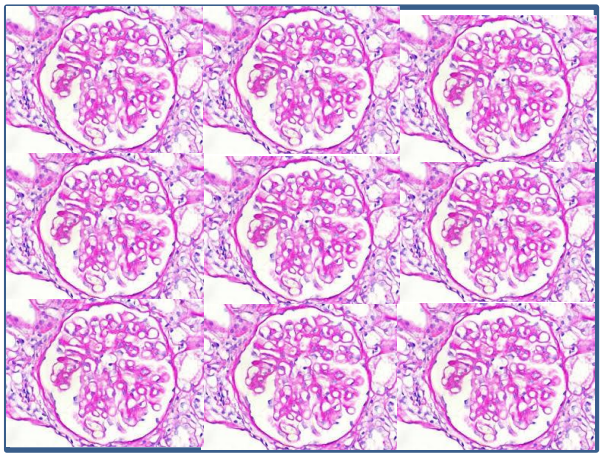


J. Bryan Carmody, and Jennifer R. Charlton Pediatrics 2013;131:1168-1179



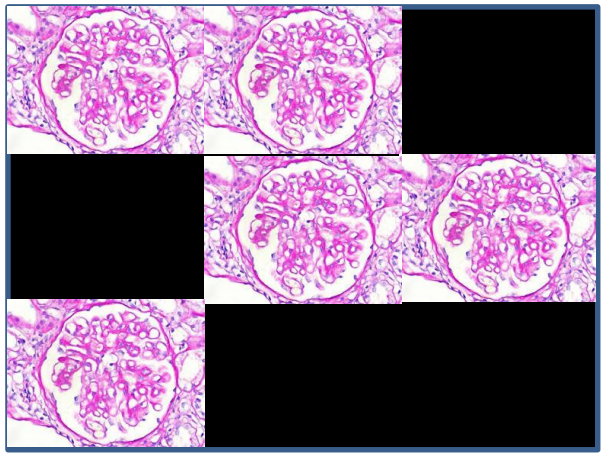
Envejecimiento

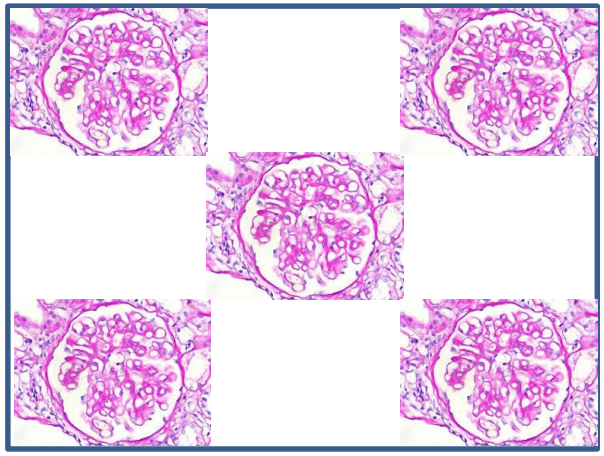




Envejecimiento

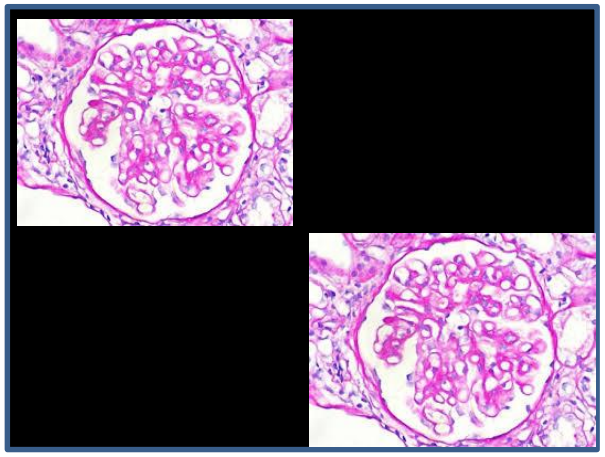
+ AKI + Nefrotóxicos





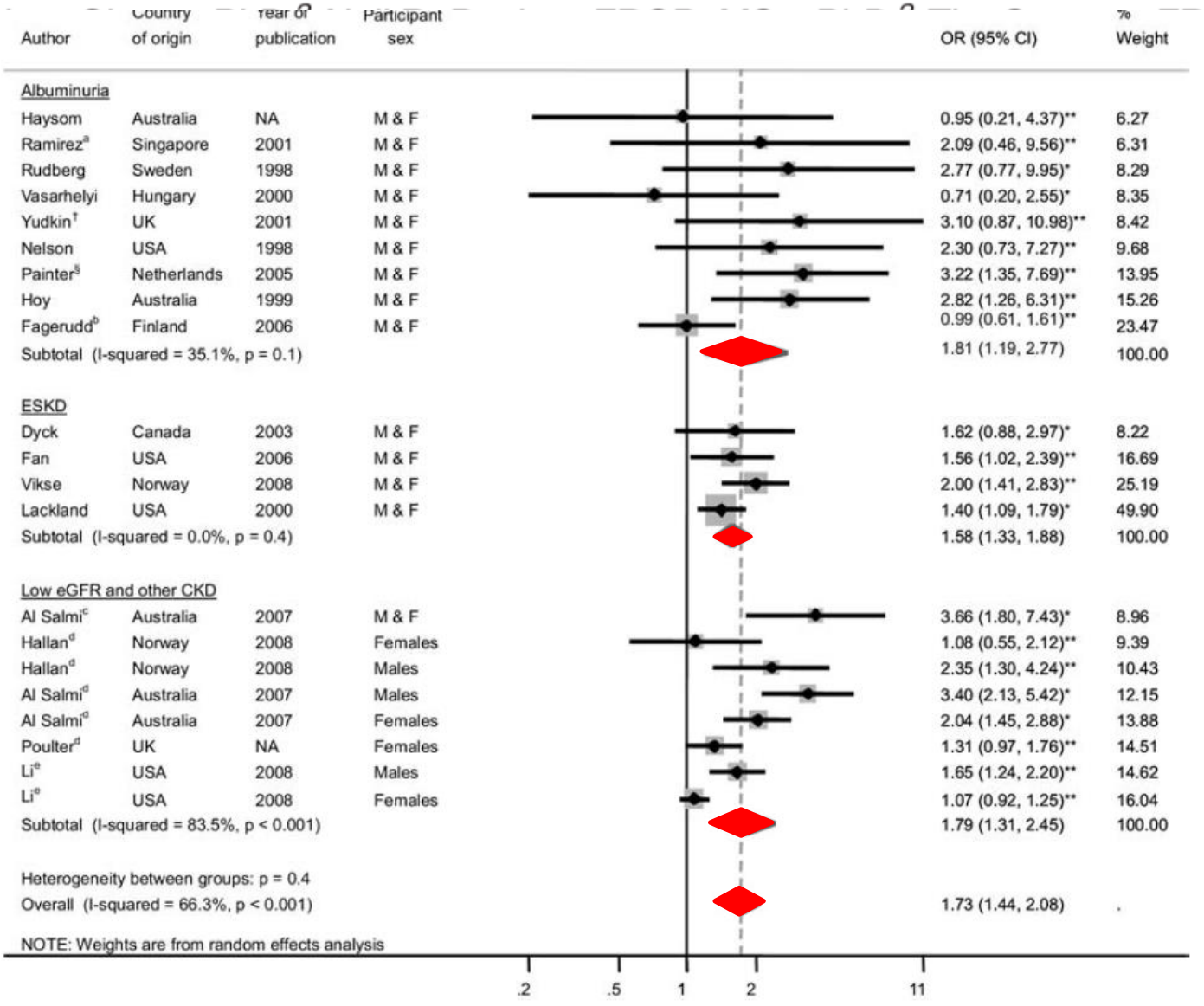
Envejecimiento

+ AKI + Nefrotóxicos



Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies

Sarah L. White, MPH,[1] Vlado Perkovic, FRACP, PhD,[1] Alan Cass, FRACP, PhD,[1]
Choon ... MD,[3]
Leigh Hay... P, MD,[6]



Preterm birth and risk of chronic kidney disease from childhood into mid-adulthood: national cohort study

Casey Crump,[1] Jan Sundquist,[2] Marilyn A Winkleby,[3] Kristina Sundquist[2]

the bmj | *BMJ* 2019;365:l1346 | doi: 10.1136/bmj.l1346

Suecia, > 4MM de RN, 1973 a 2014

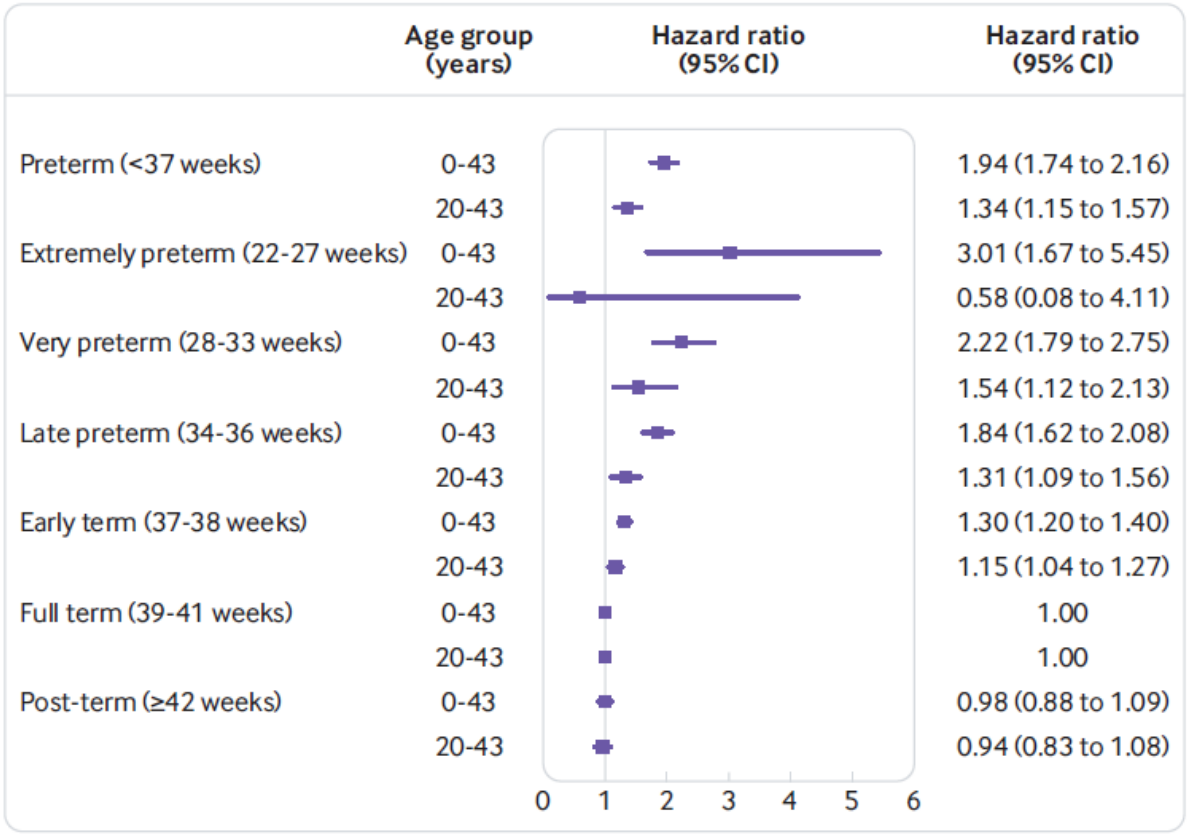


Fig 2 | Adjusted hazard ratios for chronic kidney disease at ages 0-43 and 20-43 years by gestational age at birth compared with full term birth, Sweden, 1973-2015. Whiskers are 95% confidence intervals

Journal of Nephrology
https://doi.org/10.1007/s40620-018-0473-7

ORIGINAL ARTICLE

Low birth weight is a conditioning factor for podocyte alteration and steroid dependance in children with nephrotic syndrome

Giovanni Conti[1] · Dominique De Vivo[1] · Claudia Fede[1] · Stefania Arasi[1] · Angela Alibrandi[2] · Roberto Chimenz[1] · Domenico Santoro[3]

Table 1 Main demographic and clinical characteristics of study population according to birth weight

	LBW (n = 21)	NBW (n = 68)
Male	13	43
Age at onset of NS (months)	55	53
Follow-up period (years)	7.4	7.7
Cortico-resistance, n (%)	8 (38)	5 (7)
Cortico-sensitivity, n (%)	13 (62)	63 (93)
Renal biopsy, n (%)	8 (38)	5 (7)
Focal segmental glomerulosclerosis, n (%)	8 (38)	4 (6)

p<0.03

NBW normal birth weight, *LBW* low birth weight, *NS* nephrotic syndrome

Journal of Nephrology
https://doi.org/10.1007/s40620-018-0473-7

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Low birth weight is a conditioning factor for podocyte alteration and steroid dependance in children with nephrotic syndrome

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89 niños con SN idiopático → 21 niños BPN

Table 2 Clinical course of study participants with cortico-sensitive nephrotic syndrome (CSNS) (n = 76) according to low vs. normal birth weight

	LBW (n = 13)	NBW (n = 63)
No relapse, n (%)	1 (7.7)	17 (27)
Non-frequent relapses, n (%)	2 (15.4)	18 (28.6)
Cortico-dependence, n (%)	10 (76.9)[a]	28 (44.4)
Cortico-dependent patients treated with immunosuppressive drugs, n (%)	8/10 (80)[b]	20/28 (71.4)

NBW normal birth weight, *LBW* low birth weight, *OR* odds ratio, *CI* confidence interval

[a]OR 4.744; 95% CI 1.188–18.936; $\chi^2 = 4.158$, $p < 0.05$

[b]OR = 4; 95% CI = 1.153–13.877; $\chi^2 = 3.842$, $p = 0.05$

Nephron Clin Pract. 2017 Apr; 136(1): 3–49.
Published online 2017 Mar 21. doi: 10.1159/000457967
PMCID: PMC5472217
PMID: 28319949

The Impact of Kidney Development on the Life Course: A Consensus Document for Action

The Low Birth Weight and Nephron Number Working Group

Table 7

Examples of primary kidney diseases that progress more rapidly in patients with low birth weight (LBW)

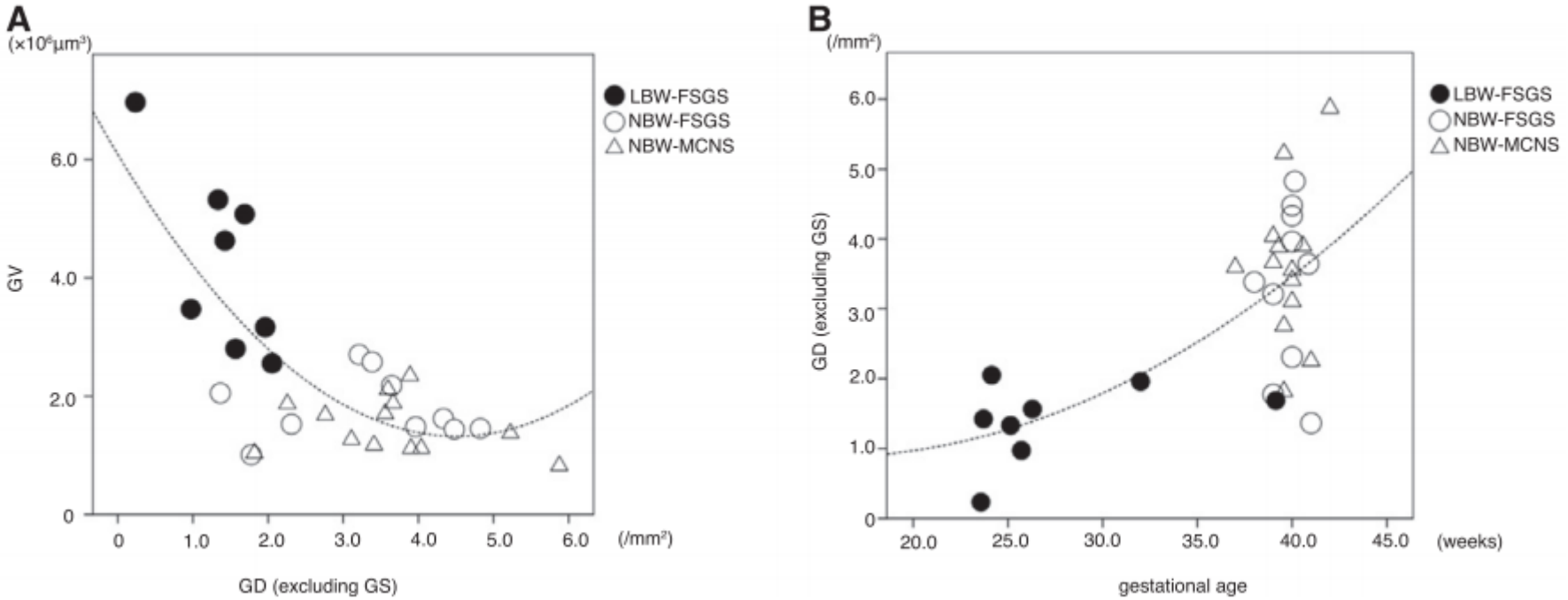
Clinical findings
IgA nephropathy [172, 173]
Increased hypertension and glomerulosclerosis in LBW children Increased progression to end-stage renal disease if LBW and/or small for gestational age, especially among males
Membranous nephropathy [181]
LBW associated with steeper decline in glomerular filtration rate
Minimal change disease [172, 174, 177]
More relapses and steroid dependence in LBW children
Chronic pyelonephritis [179]
Patients with progressive deterioration in renal function had lower birth weight
Autosomal dominant polycystic kidney disease [178]
Earlier onset of end-stage renal disease with lower birth weight
Focal-segmental glomerulosclerosis [180]
Very LBW and preterm birth are risk factors for focal-segmental glomerulosclerosis
Alport syndrome [182]
More rapid progression in LBW identical twin

Glomerular Density and Volume in Renal Biopsy Specimens of Children with Proteinuria Relative to Preterm Birth and Gestational Age

Kentaro Koike, Yohei Ikezumi,† Nobuo Tsuboi,* Go Kanzaki,* Kotaro Haruhara,* Yusuke Okabayashi,* Takaya Sasaki,* Makoto Ogura,* Akihiko Saitoh,† and Takashi Yokoo**

31 niños edad promedio 11 años

8 LBW-FSGS vs. 10 NBW-FSGS vs 13 NBW-MCNS



CJASN. 2017

Stritzke et al. Molecular and Cellular Pediatrics (2017) 4:2
DOI 10.1186/s40348-016-0068-0

Molecular and Cellular Pediatrics

REVIEW Open Access

Renal consequences of preterm birth

Amelie Stritzke[1*], Sumesh Thomas[2], Harish Amin[3], Christoph Fusch[4,5] and Abhay Lodha[6]

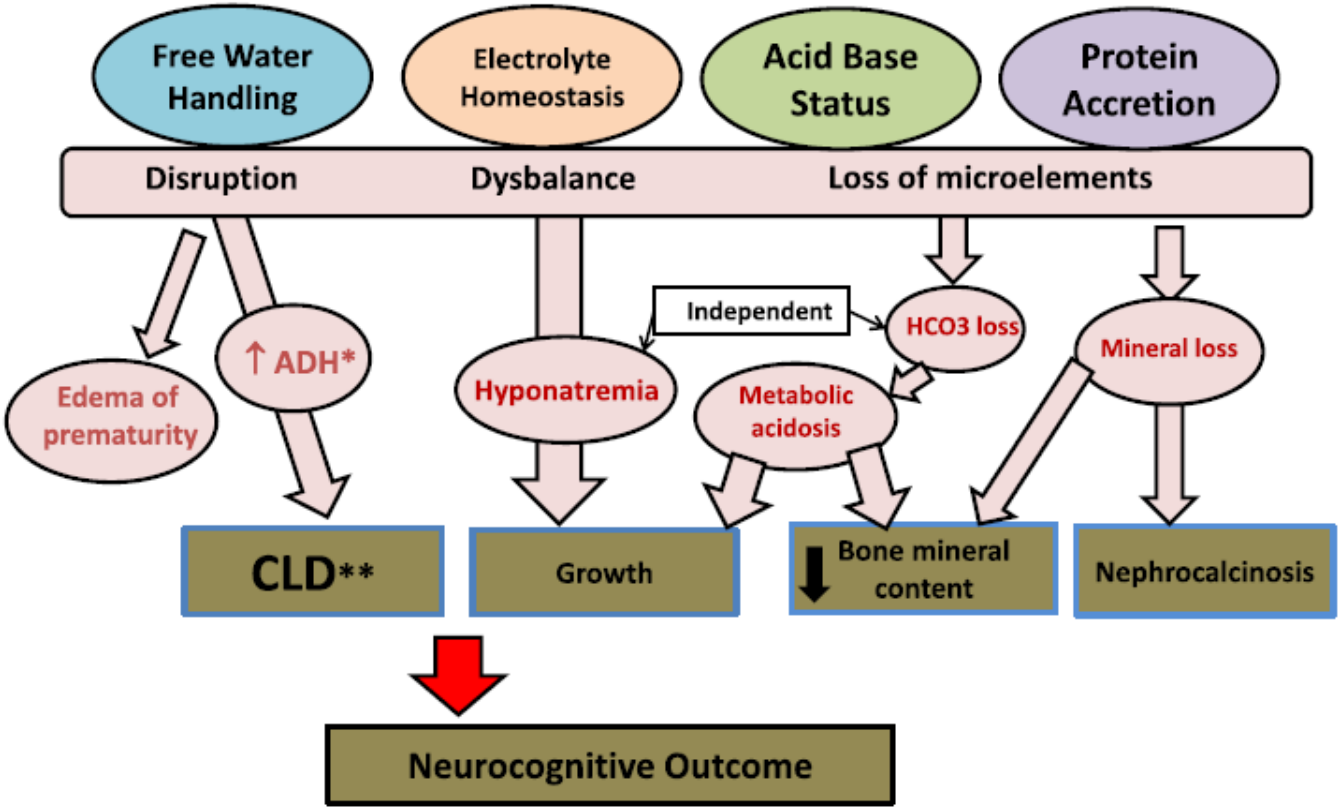
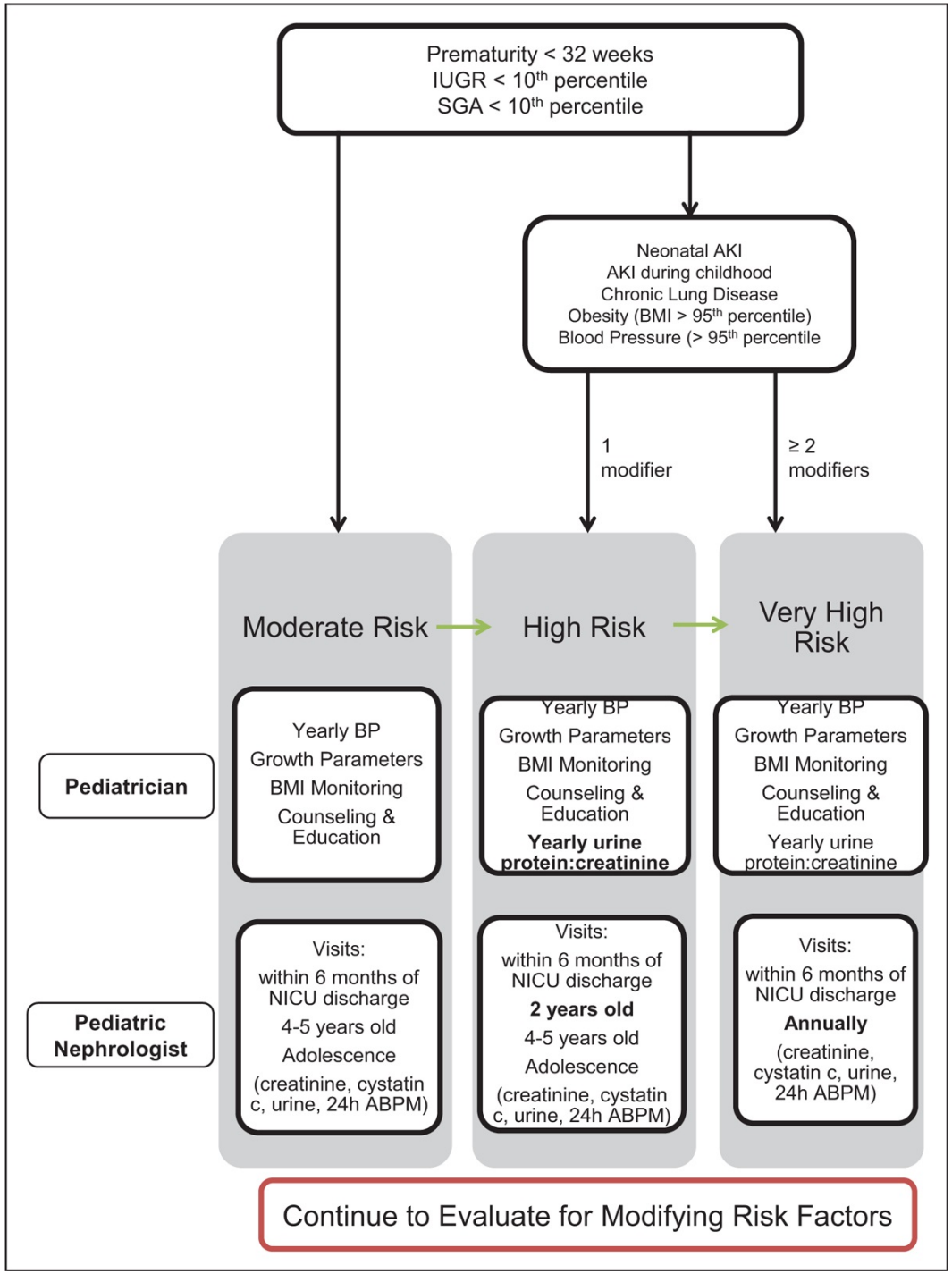


Fig. 2 Renal outcomes in prematurity

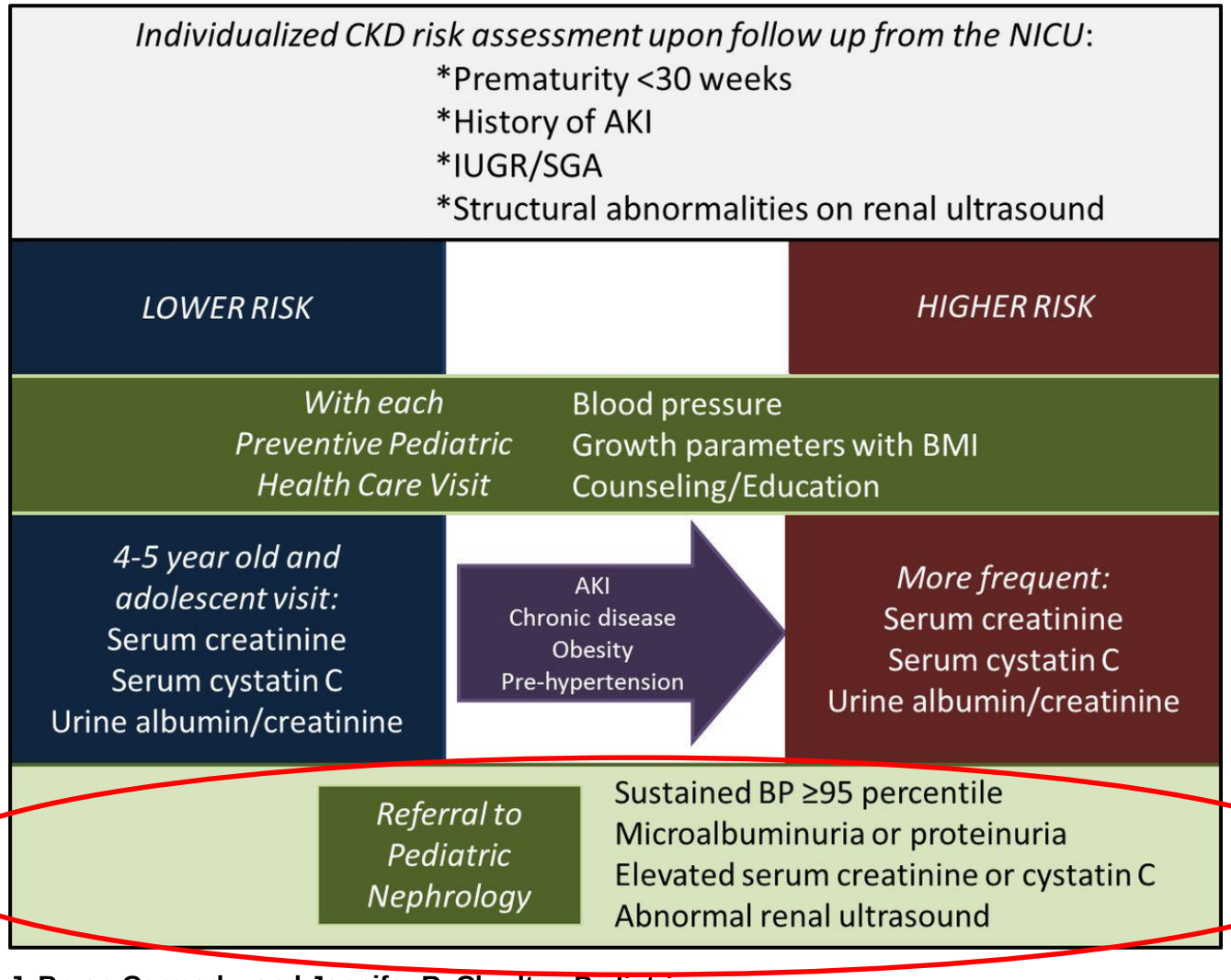


Recommended strategy for evaluation of renal dysfunction in premature infants.

Starr M, Hingorani S.

Current Opinion in Pediatrics, 2018; 30:228-235

Follow up strategies for NICU graduates.



J. Bryan Carmody, and Jennifer R. Charlton Pediatrics 2013;131:1168-1179

PEDIATRICS®

Recomendaciones para preservar fx renal en prematuros

- **Incluir historia perinatal en anamnesis a cualquier edad, y gatillar acciones preventivas en aquellos nacidos prematuros.**
- **Aconsejar que eviten potenciales nefrotóxicos (ej. AINEs) y otros factores agravantes (deshidratación, ITUR).**
- **Mantener P° Arterial bien controladas.**
- **Reducir otros factores de riesgode ERC, incluyendo obesidad, diabetes, dislipidemia, anemia y tabaco.**
- **Monitoreo periódico de fx renal con Creatinina, Cistatina C ó MAU basado en evaluación de riesgo individual.**
- **Para los potenciales donantes vivos de riñón, cautela porque tienen mayor susceptibilidad para disfunción renal en el riñón remanente.**

Conclusiones

- Nacer preT y/o BPN afecta el desarrollo y maduración del sistema CV y renal, efectos que pueden verse a largo plazo.
- Considerarlos en grupos de riesgo de HTA, CKD y podocitopatías. ¿donante vivo?
- Eventos peri y post natales pueden ser “2º hit”.
- Hay suficiente evidencia para recomendar un seguimiento específico y a largo plazo de personas que nacen prematuramente.