Prematurity: A risk factor for progression of kidney disease?

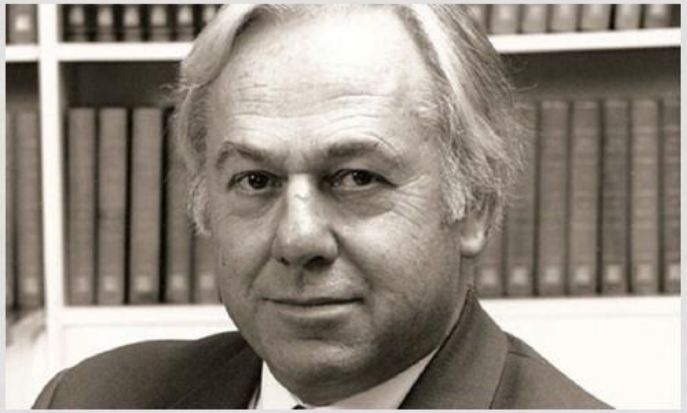
Carolyn Abitbol, M.D.
University of Miami Miller School of Medicine
/ Holtz Children's Hospital

Objectives

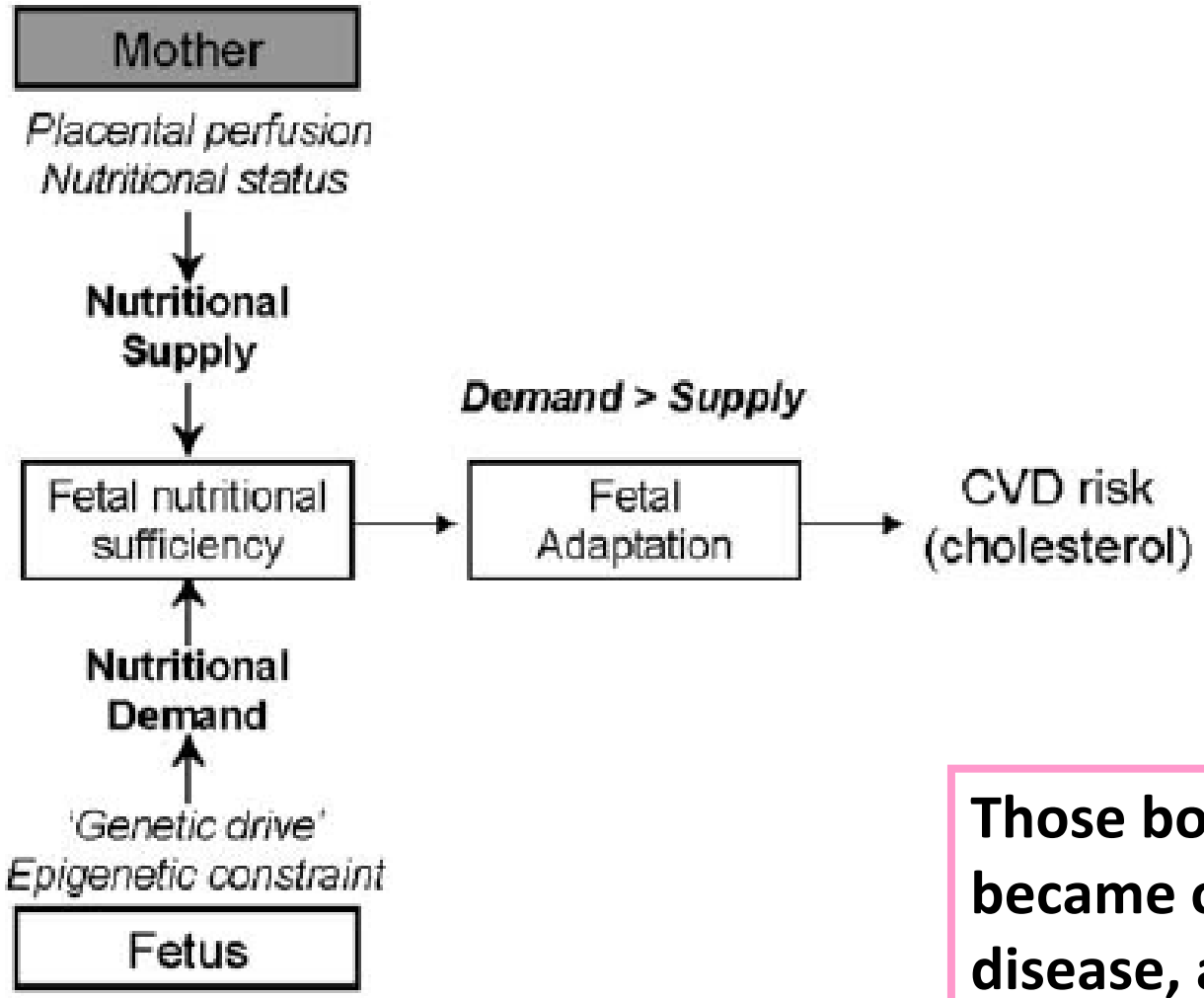
- Review nephrogenesis and the “oligonephropathy of prematurity”
- Know how to assess “normal renal function” in term & preterm infants
- Understand nephron mass and individual longevity (relative to gestational age)
- How to assess renal mass as a tool for management & prognosis

Developmental origins of health and disease

David Barker MD PhD



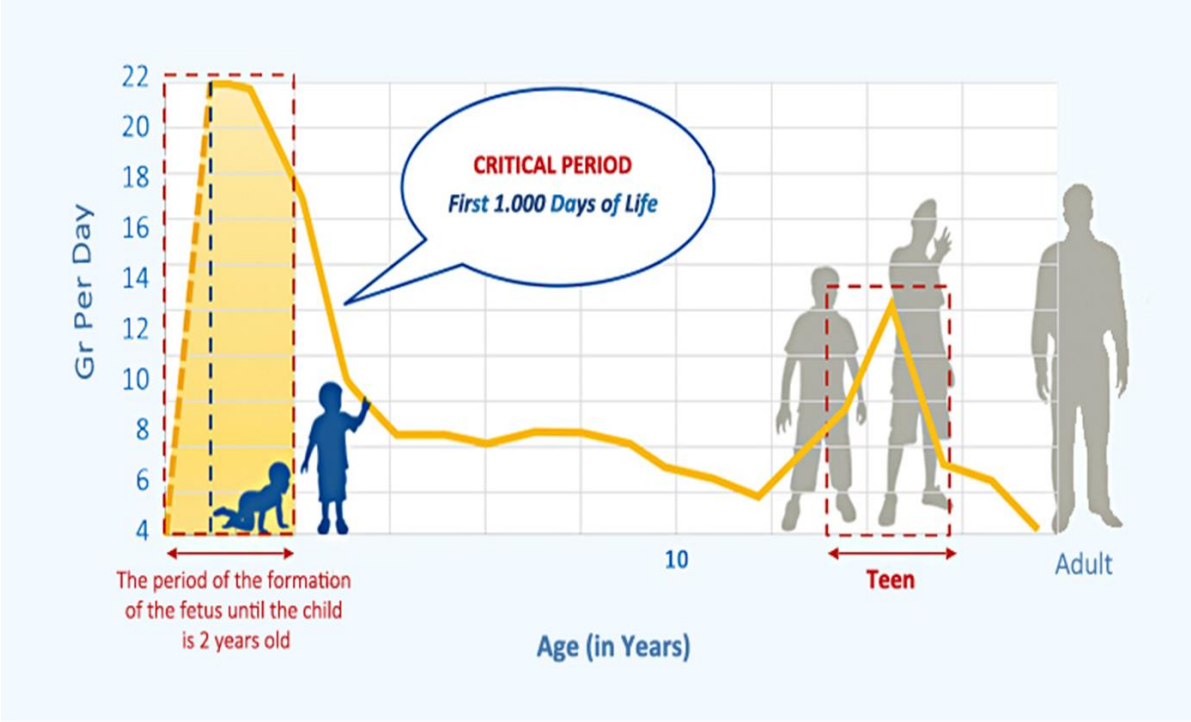
Epidemiologist who proposed the idea that common chronic diseases result not always from bad genes and an unhealthy adult lifestyle, but from poor intrauterine and early postnatal health.

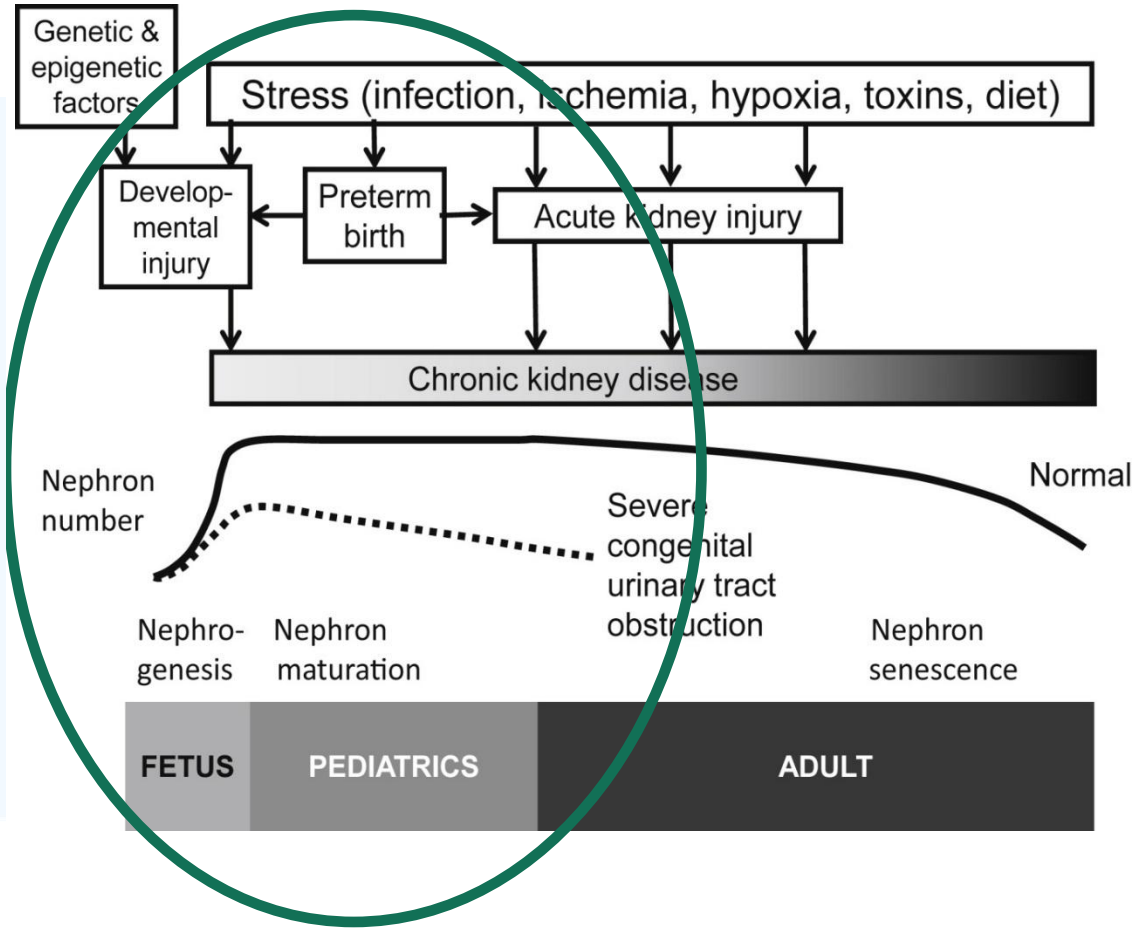


Hungry hopefuls: a Dutch food queue in 1945.

Those born after the Dutch famine became obese, developed T2DM, kidney disease, and passed it to 3 generations.

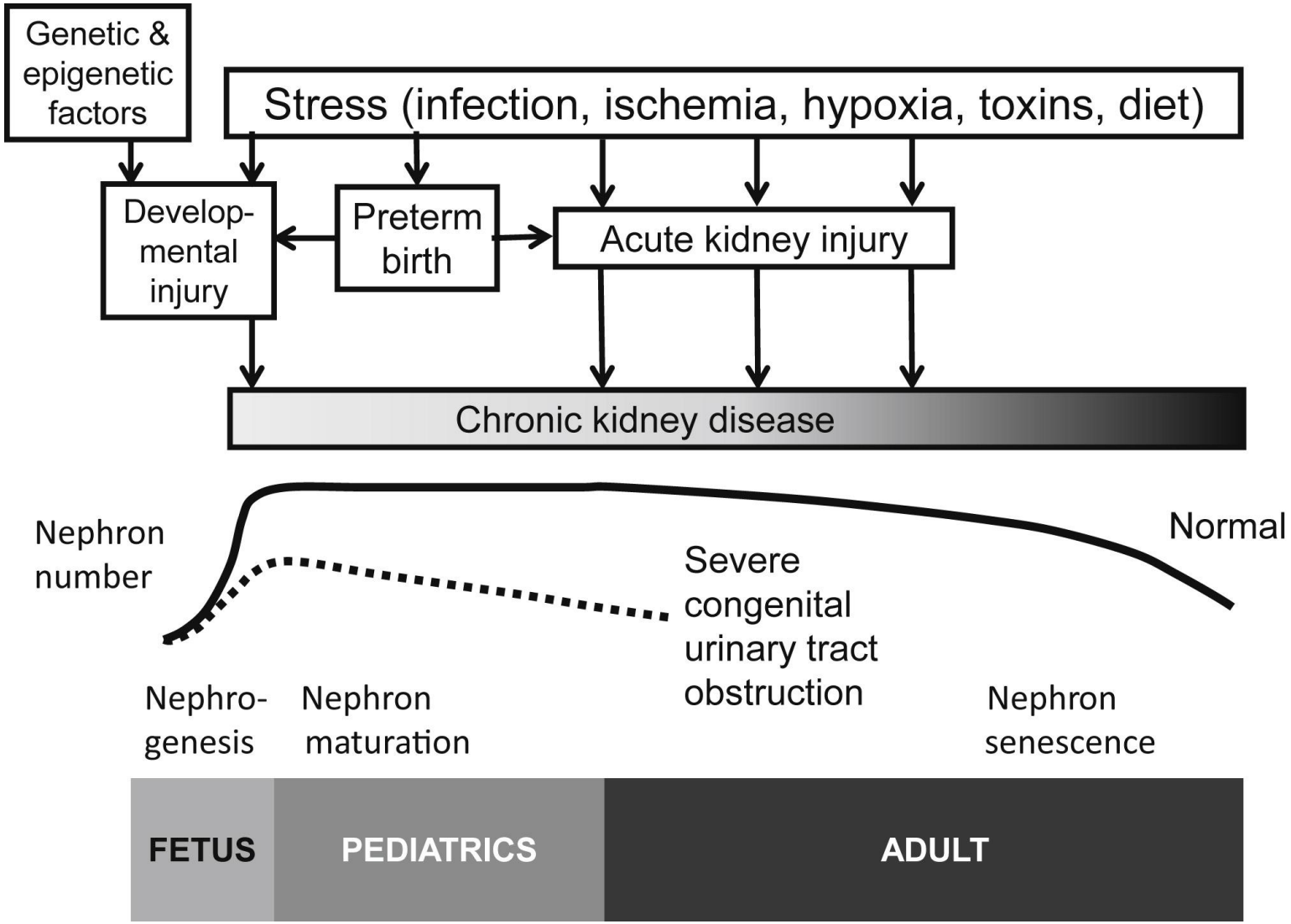
The First 1000 Days: Conception through 2 years



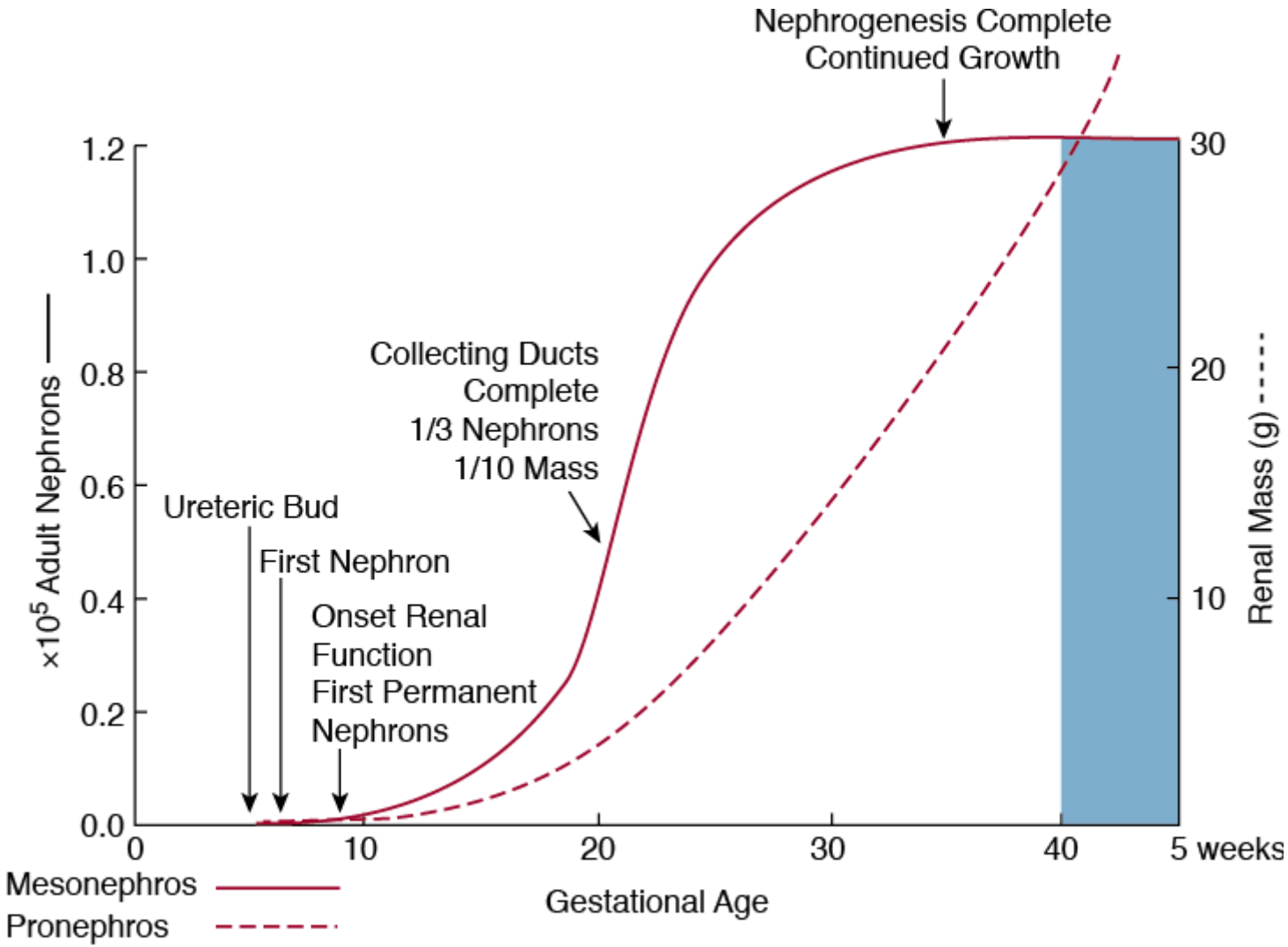


GFR INCREASES FROM 25% TO 100% BY 2 YEARS OF AGE

The Life Cycle with CKD

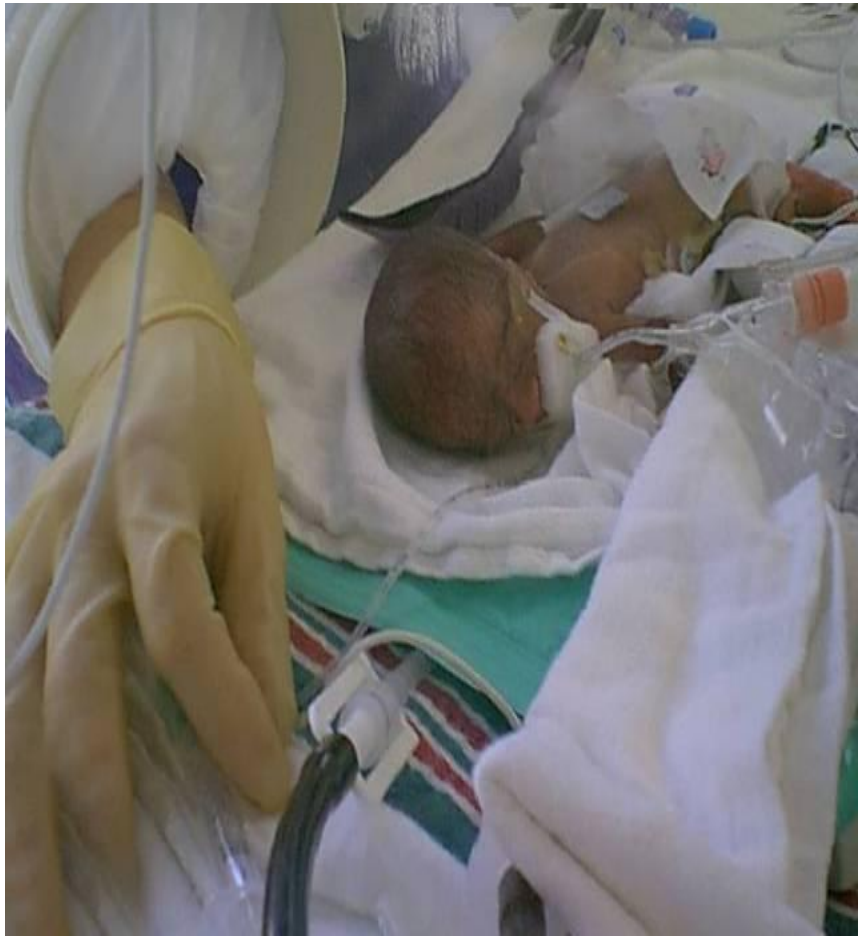


Nephrogenesis is complete in utero



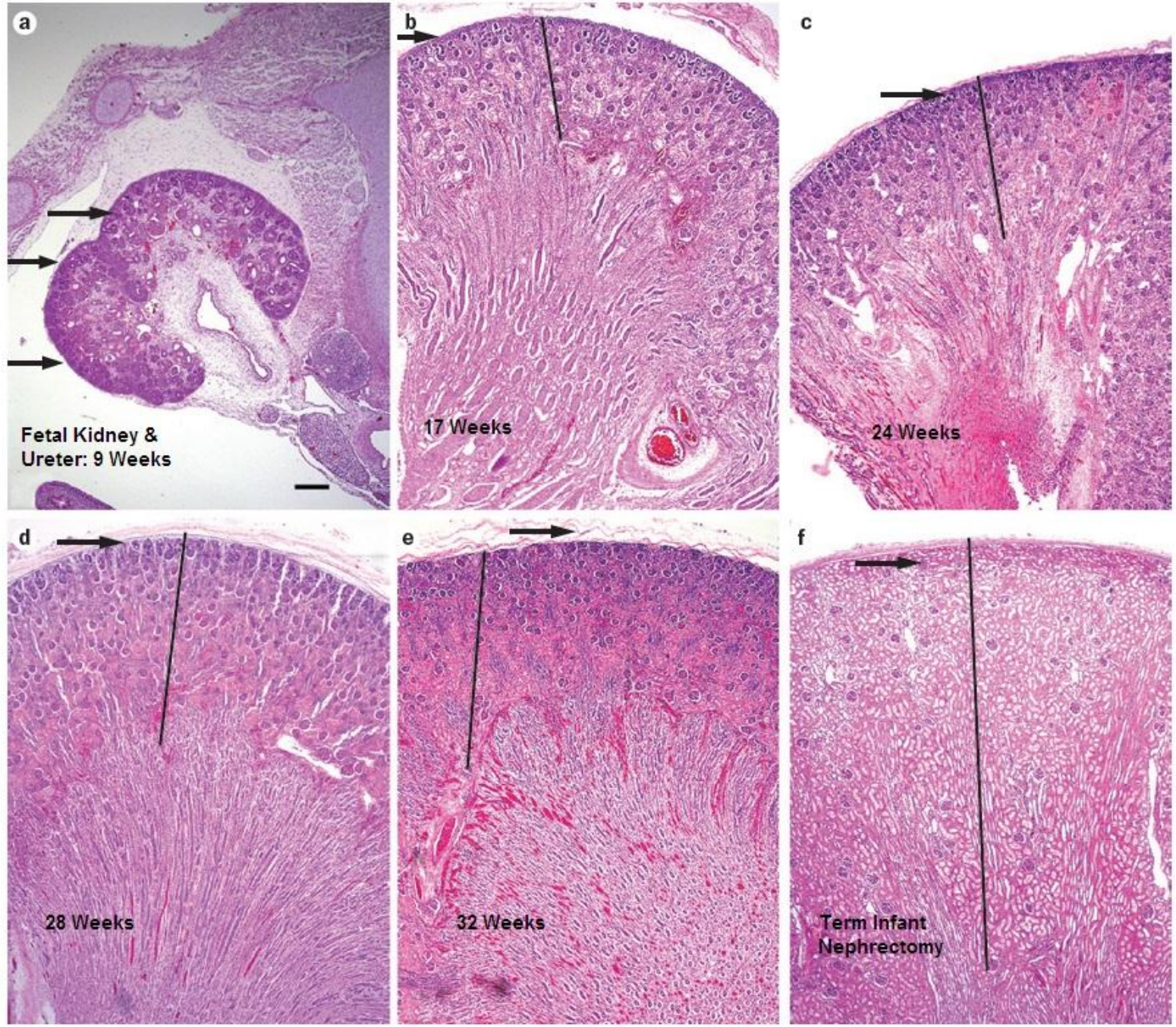
Prematurity & Cardio Renal Disease

- **Preterm birth: 9-14% of pregnancies in the US. 6% in Europe**
- **Limit of Viability is currently extended to 23 weeks GA**
- **Long term survival has increased substantially during the past 40 years.**
- **30% of Preterm births are associated with gestational HT.**
- **Twins now comprise 3-5% of pregnancies with 60% of twins born preterm.**
- **15-20% of the ESRD program is comprised of those born <2500 grams.**



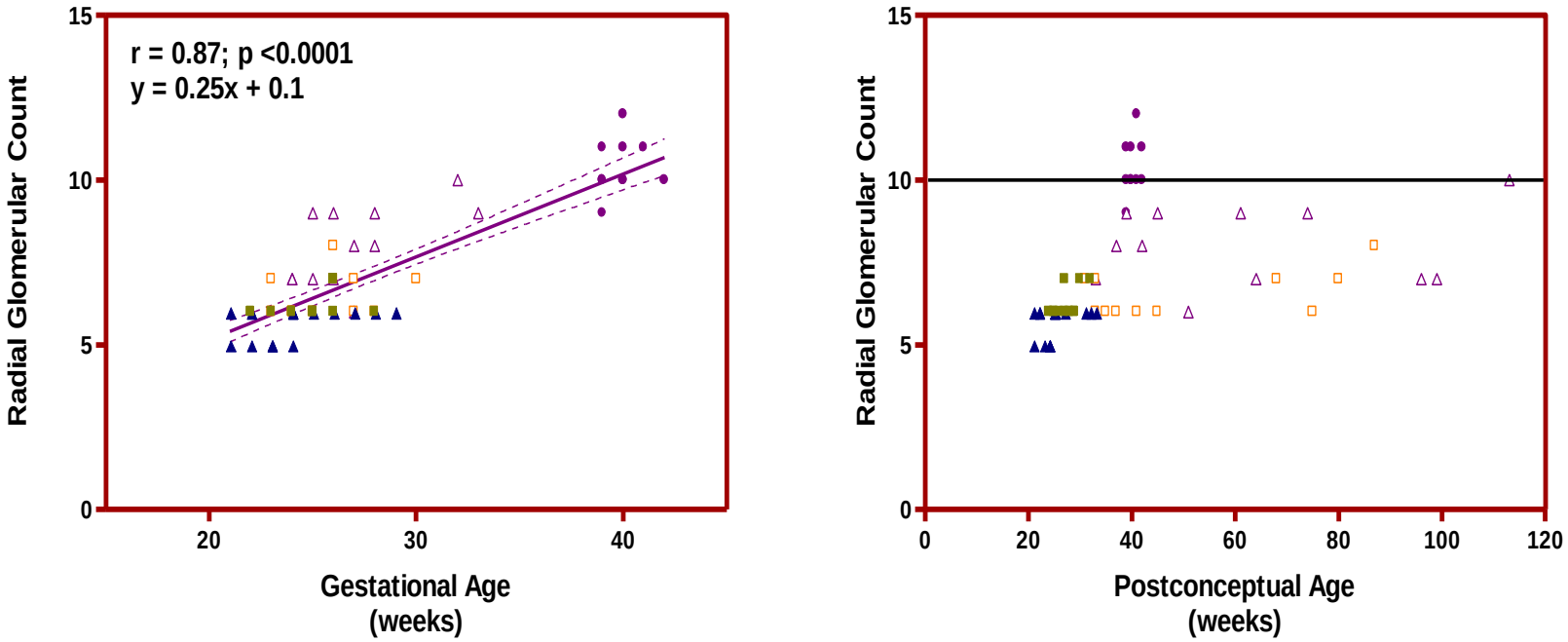
Hypothesis:

Preterm birth provides a human model of developmental programming of cardiovascular and kidney disease in adult life.



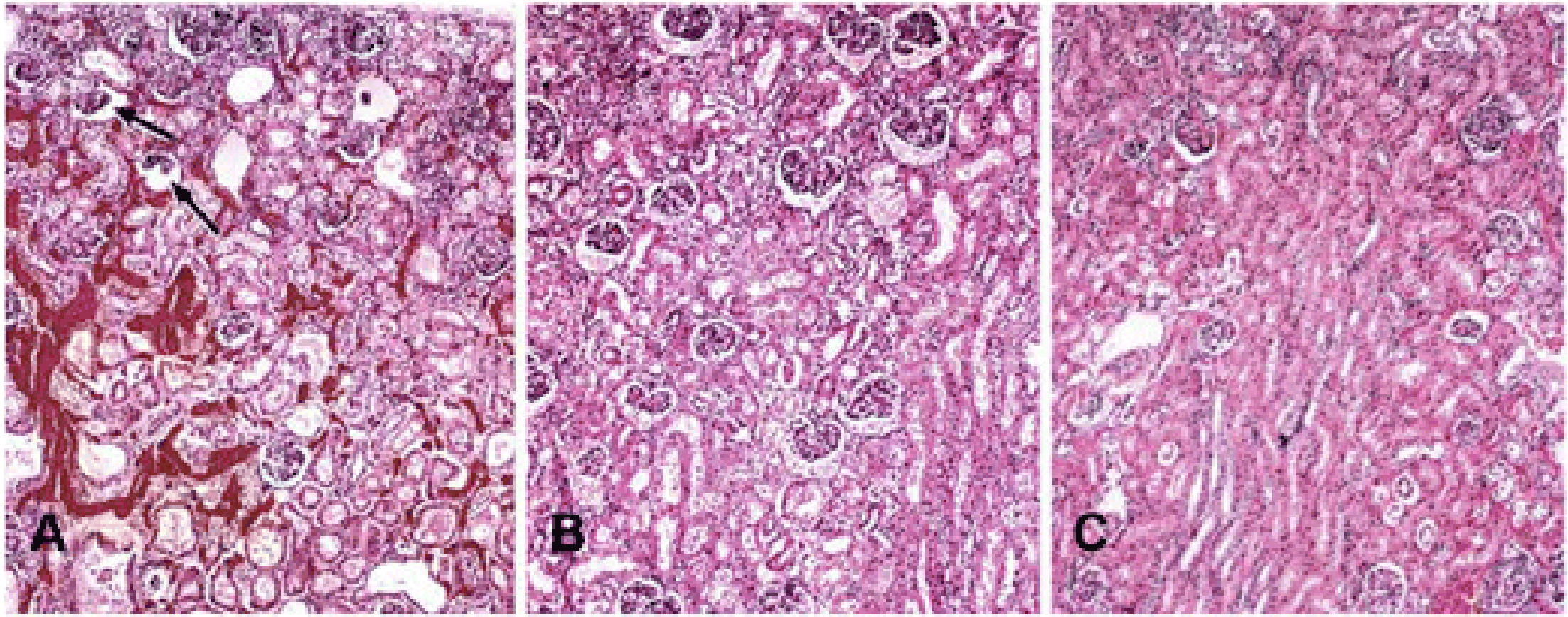
Abitbol, C. L. & Rodriguez, M. M. *Nat. Rev. Nephrol.*

Graphs of Radial Glomerular Counts by Gestational Age and Post-Conceptual Age



1. Nephrogenesis continued for up to 40 post-natal days; but the extreme preterm infants never achieved a full complement of radial glomerular generations compared to term infants.
2. Many abnormal glomeruli were formed during extra-uterine nephrogenesis, particularly in those with AKI.
3. Hyperfiltration with glomerulomegaly was evident in early infancy.

Post natal nephrogenesis in preterm infants



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

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

Premature infants <1000g
n=66
Gestational age, Postnatal age and
+/- renal failure

There were fewer "layers" of glomeruli (radial glomerular counts) premature infant kidneys than the term infant kidneys

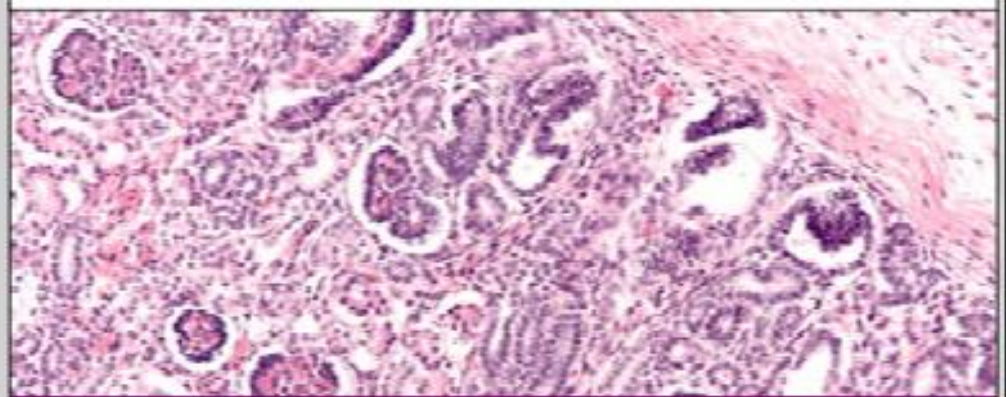
Evidence of glomerulogenesis for 40 days after birth

Increased mesangial tufts and capsule area in premature infants surviving over 40 days

CLINICAL RESEARCH www.jasn.org

Accelerated Maturation and Abnormal Morphology in the Preterm Neonatal Kidney

Megan R. Sutherland,* Lina Gubhaju,* Lynette Moore,† Alison L. Kent,‡ Jane E. Dahlstrom,§ Rosemary S. C. Horne,‖ Wendy E. Hoy,¶ John F. Bertram,* and M. Jane Black*



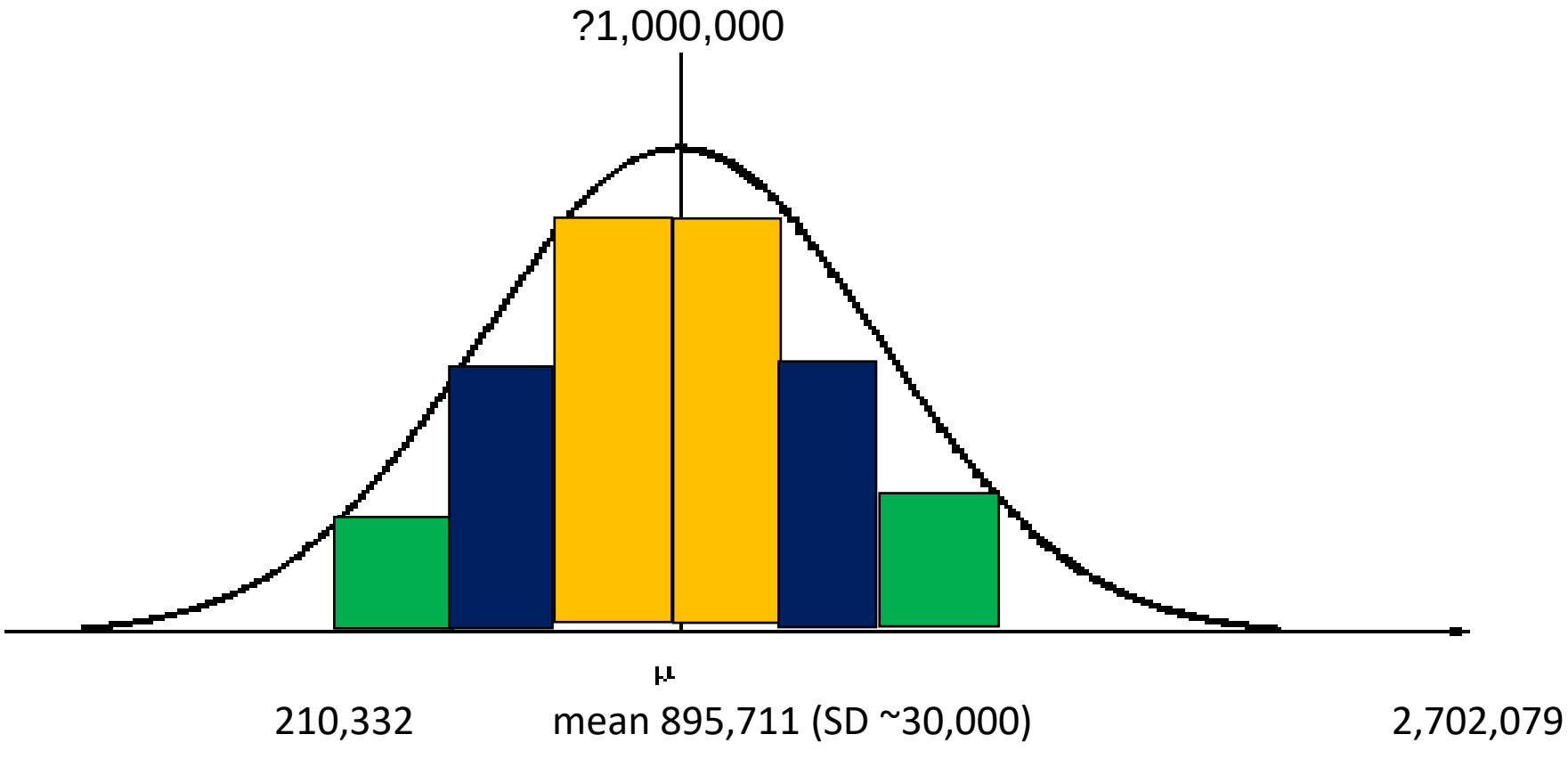
- 28 kidneys were examined from premature infants (2-68 days)
- 32 still born gestational controls
- Accelerated maturation of the kidney in the premature group
- Decreased nephrogenic zone
- More abnormal glomeruli with larger glomerular area

Human nephron endowment

Nyengaard, 1992
n=37
617,000
(331,000-1,424,000)

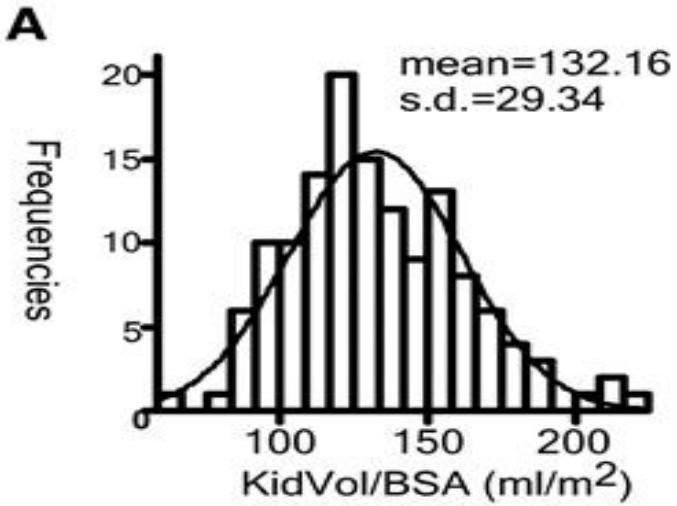
Keller, 2003
n=10
1,429,200
(800,000-2,000,000)

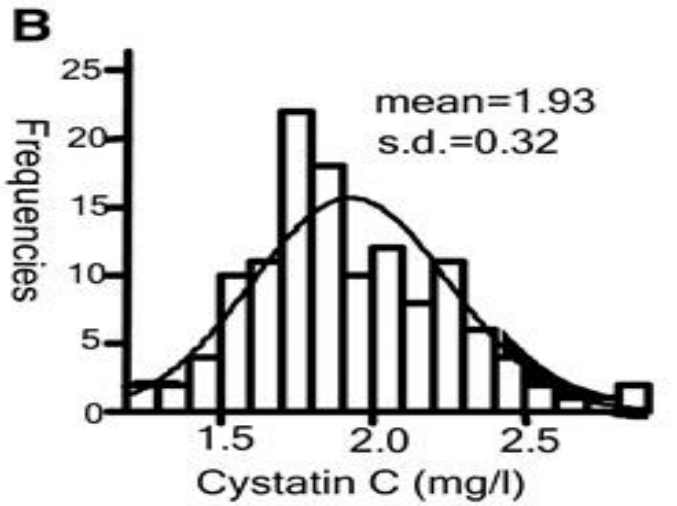
Bertram, 2011
n=398
895,711
(210,332-2,702,079)

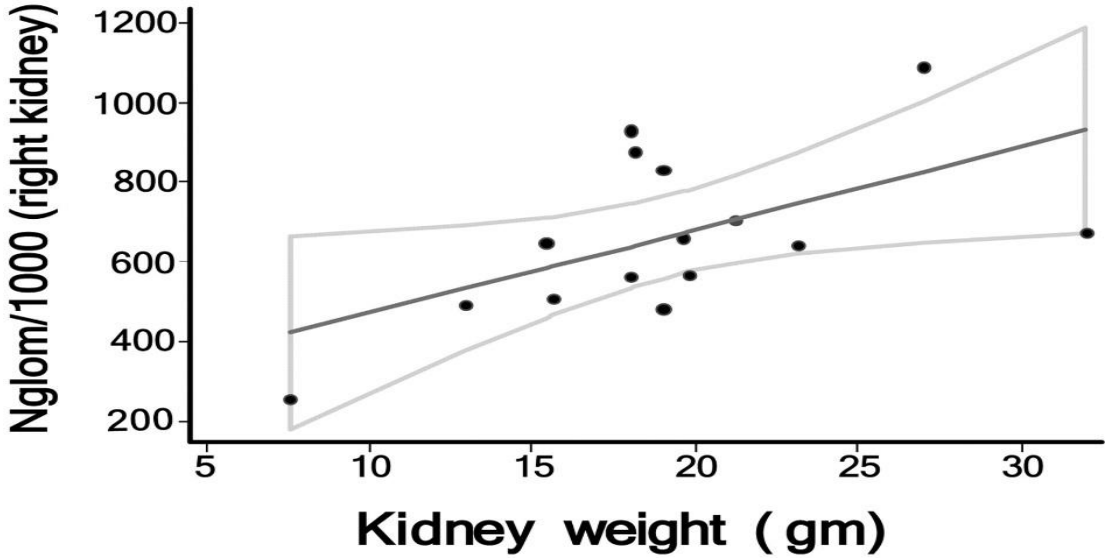


Slide Courtesy: Jennifer Charlton, MD, MSc

Clinical characteristics of the newborns of white cohort (n = 136).







C

Mean birthweight = 3.62±0.48(Kg)

Mean body surface area = 0.23±0.02(m^2)

Mean gestational age = 39.44±1.10(weeks)

Males 53%, Females 47%

Zhao Zhang et al. JASN 2008;19:2027-2034

JASN

"Averting the Legacy of Cardio-vascular & kidney Disease: Focus on the Child"

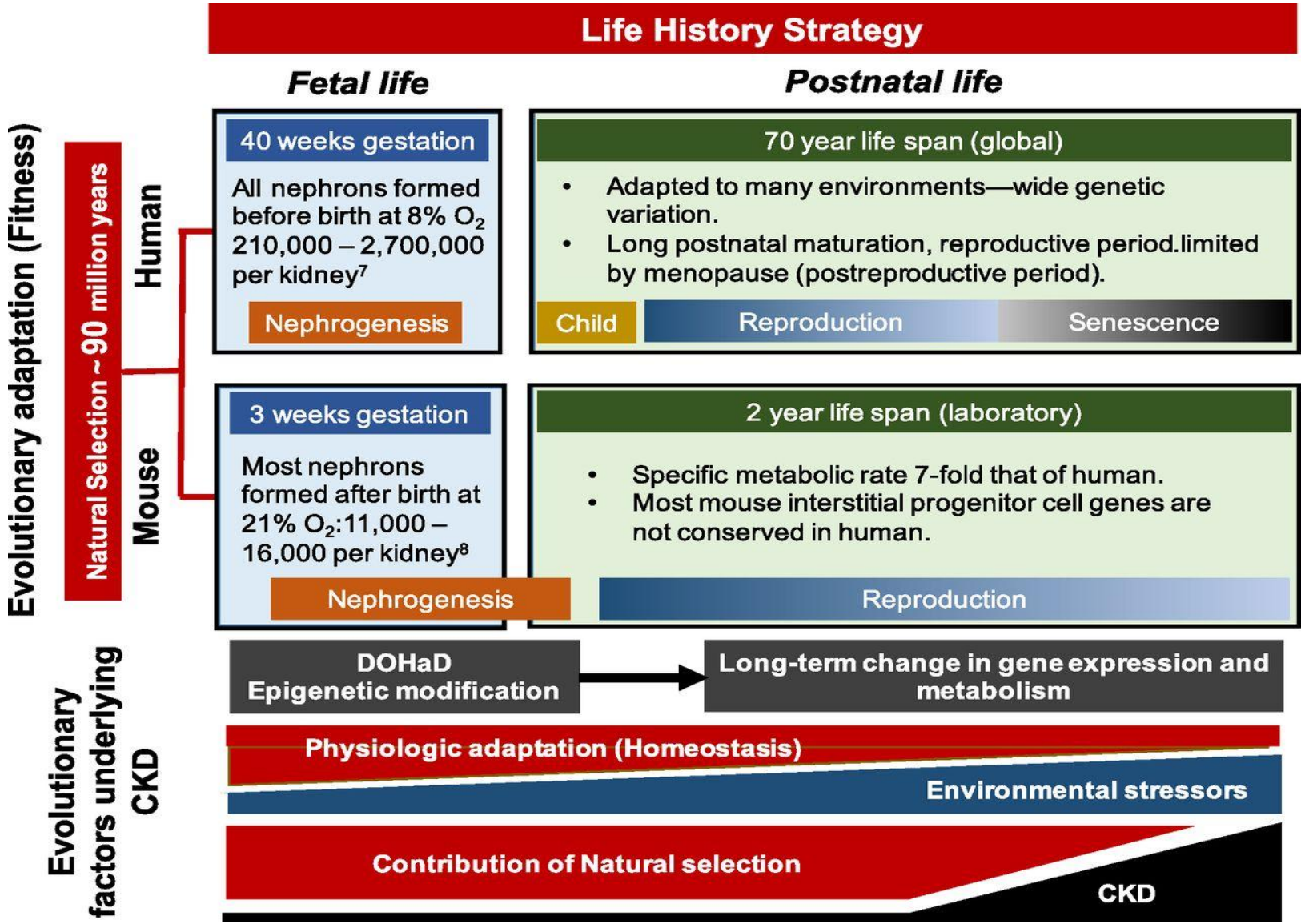
"For in every adult there dwells the child that was, and in every child there lies the adult that will be. —

John Connolly, The Book of Lost Things

Consider:

- Developmental programming and periods of *plasticity*
- The role of low birth weight and preterm birth on individual and global health
- Nephron endowment and why it is important for CVD
  - Cardio-renal Syndrome
  - *Resilience* and *senescence* and life's trajectory

Evolutionary factors play a central role in determining life history strategy, which spans fetal and postnatal life, and underlies differences between human and mouse kidney development as well as the course of CKD.



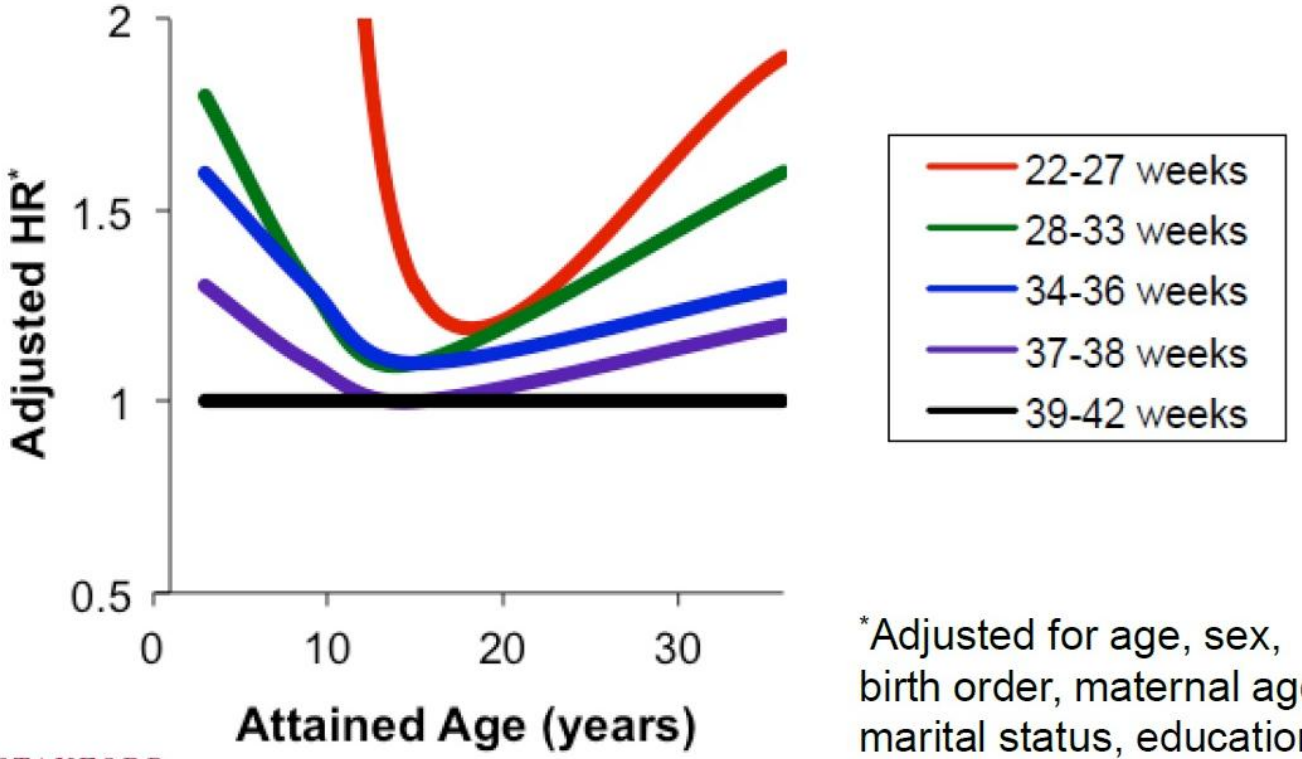
Robert L. Chevalier JASN 2018;29:706-709

JASN

Population Consequences of Improved Preterm Survival

- ~10% of births each year are preterm; 0.07% Extremely low gestational age newborns (ELGANs) Worldwide
  - 10% of 4 Million births: ~ 400,000; 98% survive: ~380,000
  - <0.07 % ~35,000
  - ~90% survive: ~30,000 VLBW each year
- 2015: US Population: ~322 million
  - ~32.2 million born preterm; 4.6 million are ELGANs
- Even a “slight” (10-20%) higher risk of ANY illness has a huge population effect

MORTALITY BY GESTATIONAL AGE AT BIRTH



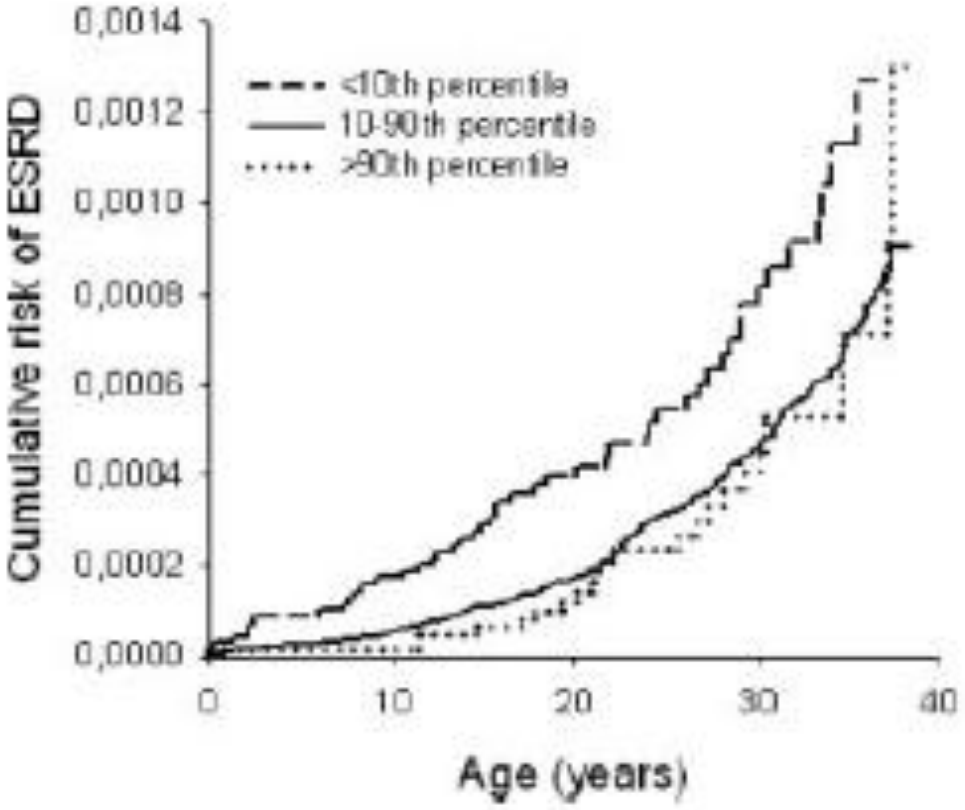
*Adjusted for age, sex, birth order, maternal age, marital status, education

STANFORD SCHOOL OF MEDICINE
Stanford University Medical Center

Swedish National Cohort Study

(Crump et al, *JAMA* 2011; 306:1233-40;
Crump et al, *Epidemiol* 2013; 24:270-6)

LBW Increases Risk of ESRD: Norwegian Birth Registry 1967-2004



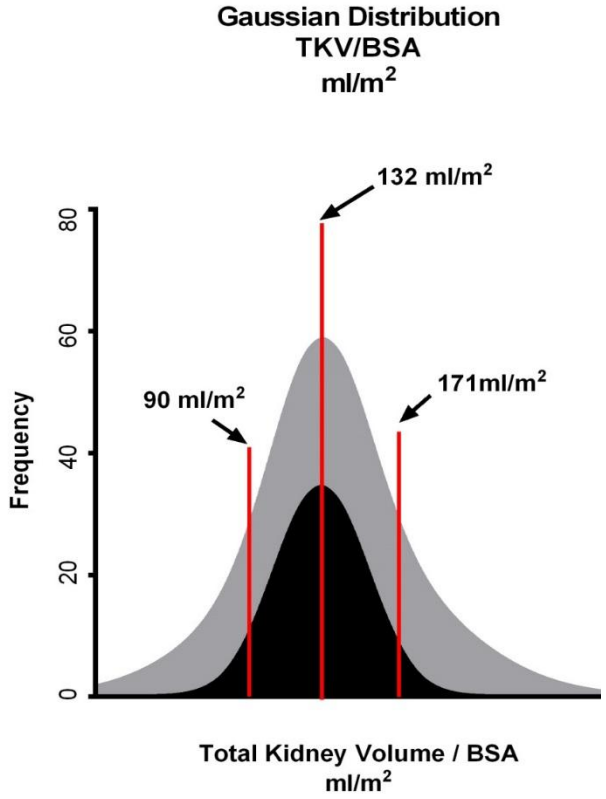
- > 2 million births
- LBW (<2500 grams)
  - RR 1.7 for ESRD
  - RR 1.5 (SGA)
- LBW more strongly associated with ESRD during the first 14 years of life (70% more likely) than > 15 years of age.

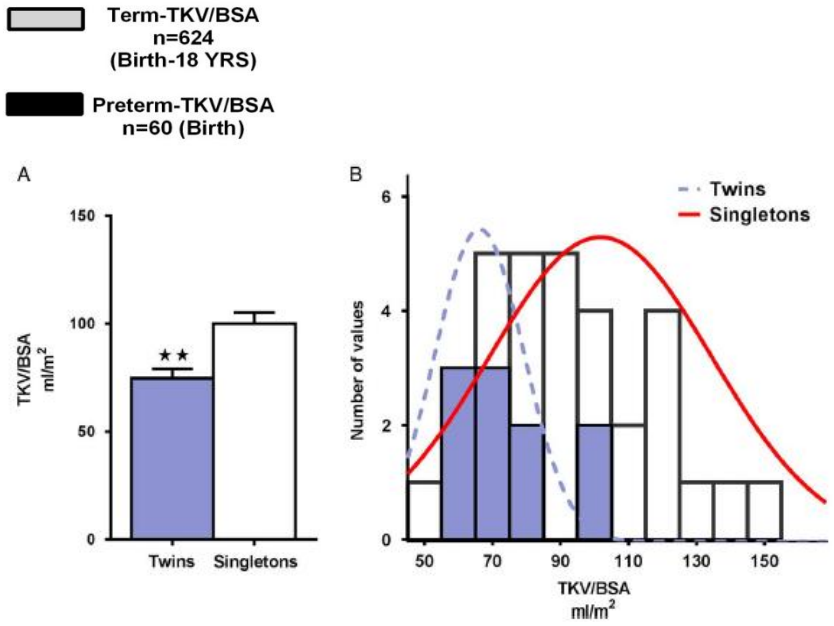
J Am Soc Nephrol 19: 151–157, 2008.

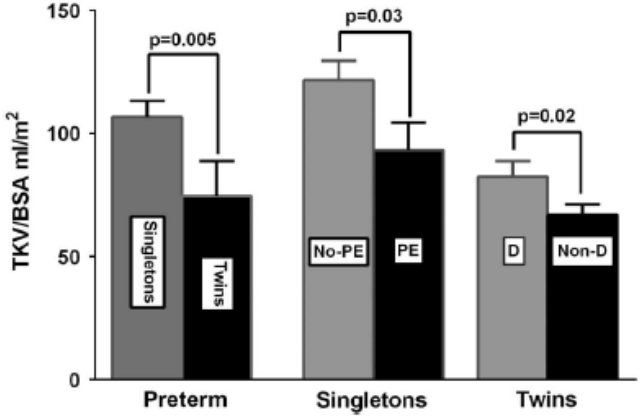
Neonatal Kidney Size and Function in Preterm Infants: What Is a True Estimate of Glomerular Filtration Rate?

Carolyn L. Abitbol, MD[1], Wacharee Seeherunvong, MD[1], Marta G. Galarza, MD[2], Chryso Katsoufis, MD[1], Denise Francoeur, RN[1], Marissa DeFreitas, MD[1], Alcia Edwards-Richards, MD[1], Vimal Master Sankar Raj, MD[1], Jayanthi Chandar, MD[1], Shahnaz Duara, MD[2], Salih Yasin, MD[3], and Gaston Zilleruelo, MD[1]

J Pediatr 2014;164:1026-31





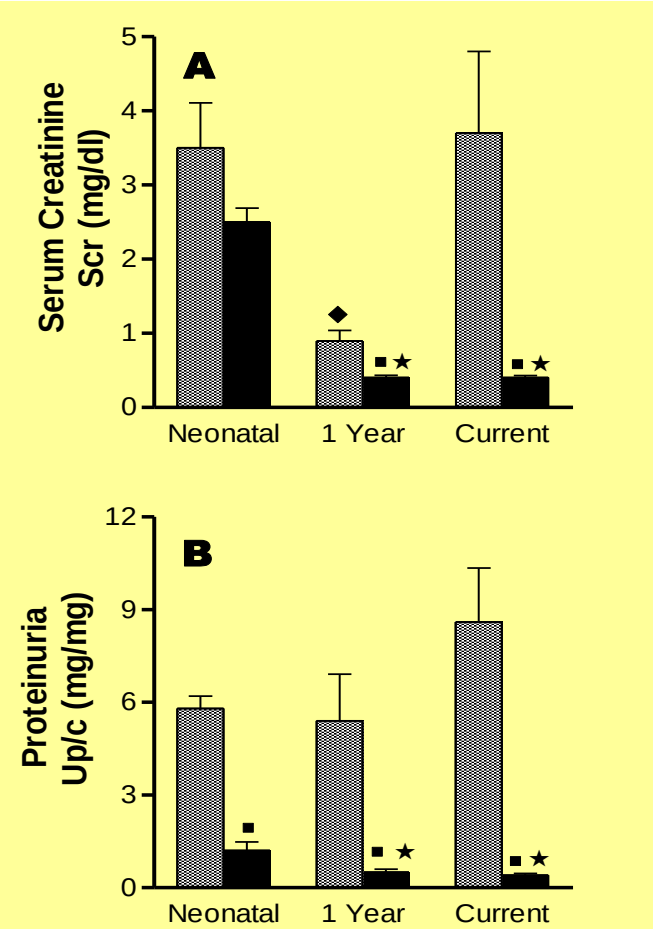


Supported by the Gerber Foundation

Conclusions

- Preterm infants exhibit reduced kidney volume and function compared to Term infants.
- The major determinants of eGFR in infants are mean arterial pressure, gestational age and total kidney volume.
- Preterm infants demonstrate lower measures of kidney function and increased proteinuria compared to Term infants.
- Cystatin C is superior to creatinine as a measure of kidney function in preterm infants.
- Creatinine underestimates eGFR in preterm infants at each level of gestational age.

Neonatal Renal Function: Progression of Renal Disease



- 20 LBW Preterm Infants with ARF in the Neonatal Period
- Average follow-up: 8±5 YRS
- 10 Developed chronic kidney disease (CKD)
- 10 Had recovery
- Initial Scr were similar at birth and improved at 1 year to <1.0 mg/dl.
- Urine pr/cr ratio was always more elevated in CKD patients.

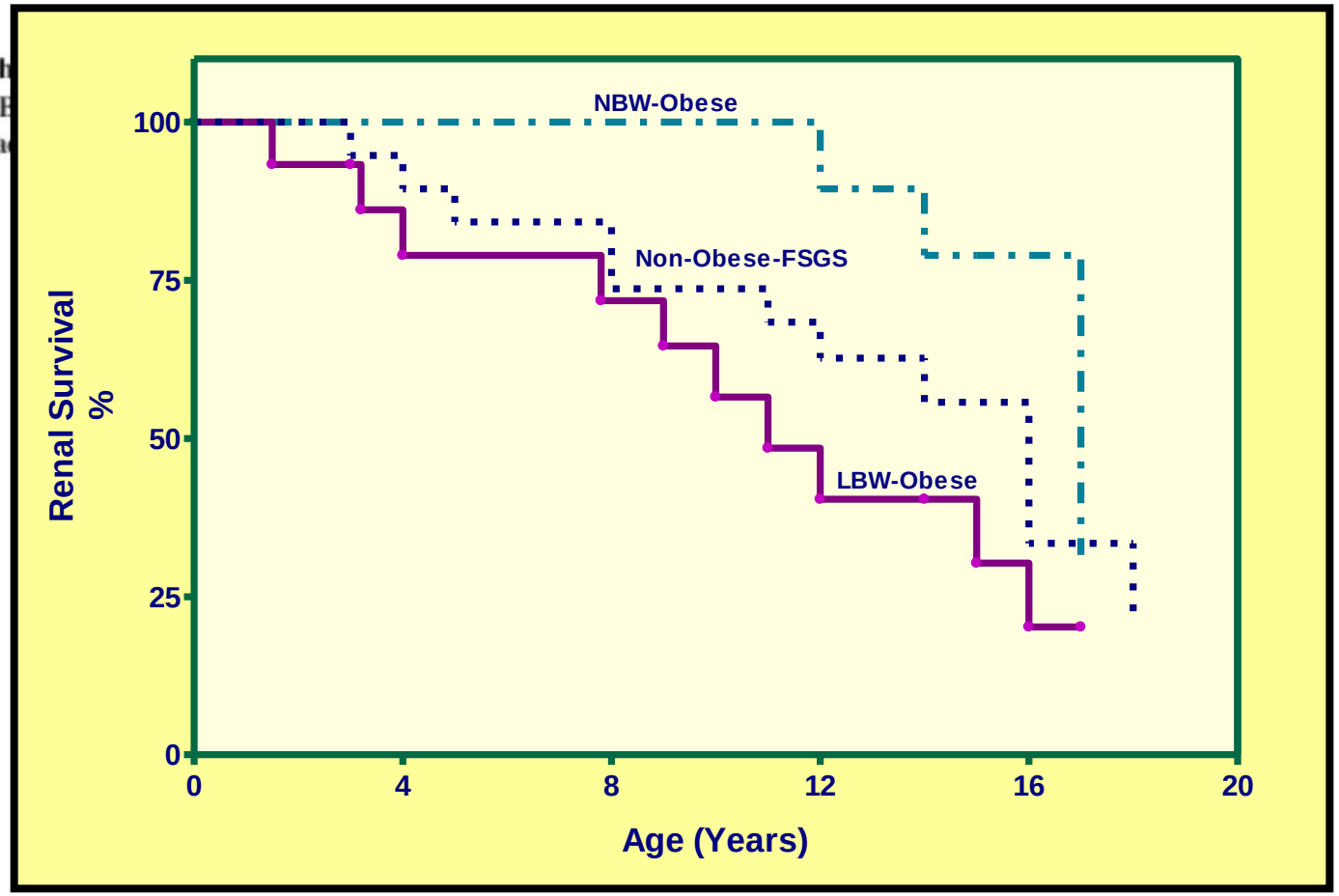
Abitbol et.al. Pediatr Nephr (2003) 18:887-893

Pediatr Nephrol (2009) 24:1363–1370
DOI 10.1007/s00467-009-1120-2

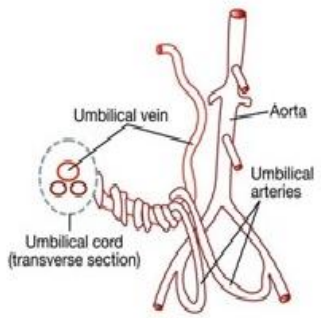
ORIGINAL ARTICLE

Obesity and preterm birth: additive risks in the progression of kidney disease in children

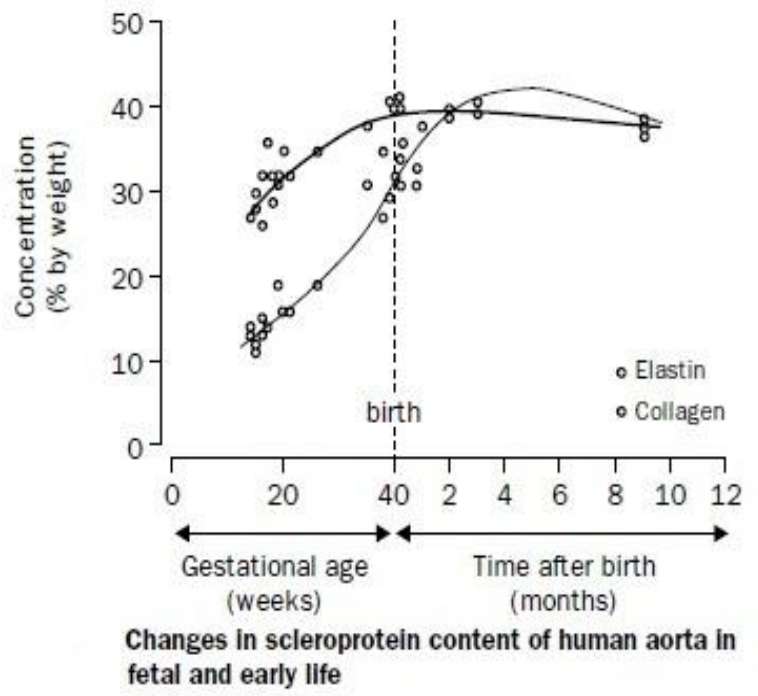
Carolyn L. Abitbol · Jayanthi Ch
Maria M. Rodríguez · Mariana E
Wacharee Seeherunvong · Micha
Gastón Zilleruelo



Umbilical Artery Histomorphometry



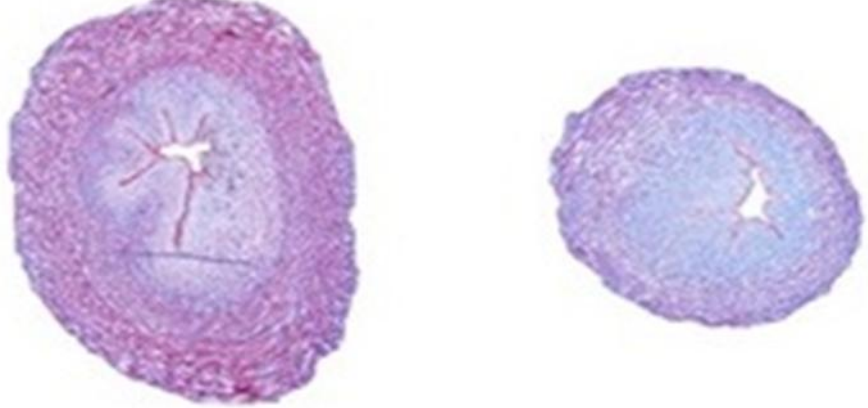
- The aorta's elastic properties depend on ***elastin*** (interspersed with muscle) which develops during fetal life. It has a 1/2 –life of 40 years.
- Collagen is associated with vascular stiffness and replaces elastin with aging.
- LBW is associated with increased vascular stiffness and hypertension in childhood and adulthood.
- Umbilical artery ***muscular (elastin)*** versus ***collagen*** density vary with the fetoplacental environment.



Changes in scleroprotein content of human aorta in fetal and early life

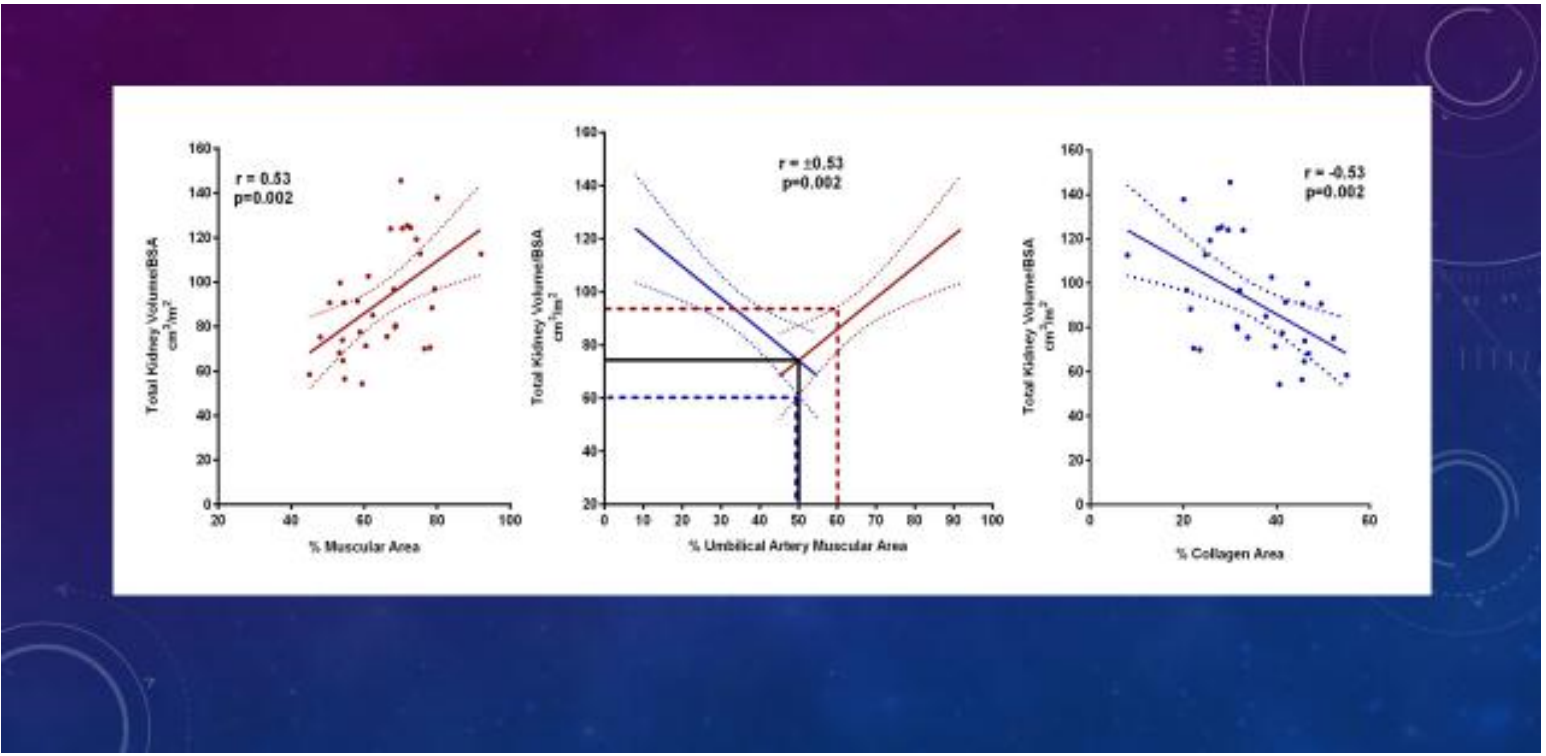
Martyn & Greenwald. *Lancet* 1997:350; 953-55

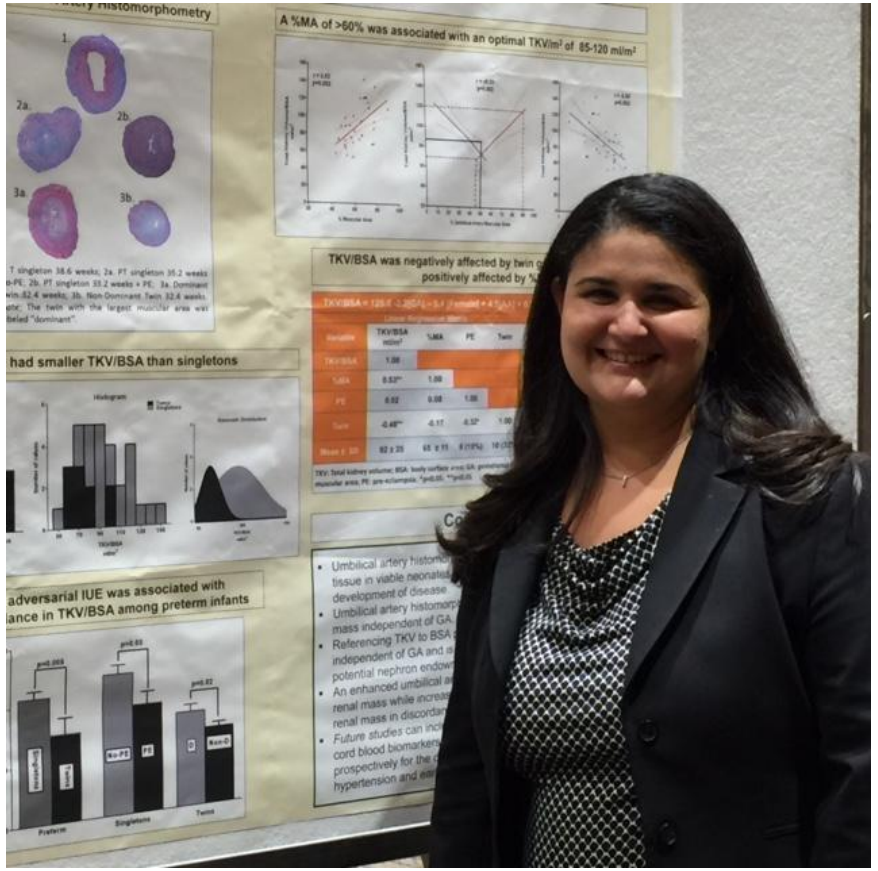
Umbilical artery histomorphometry: a link between the intrauterine environment and kidney development

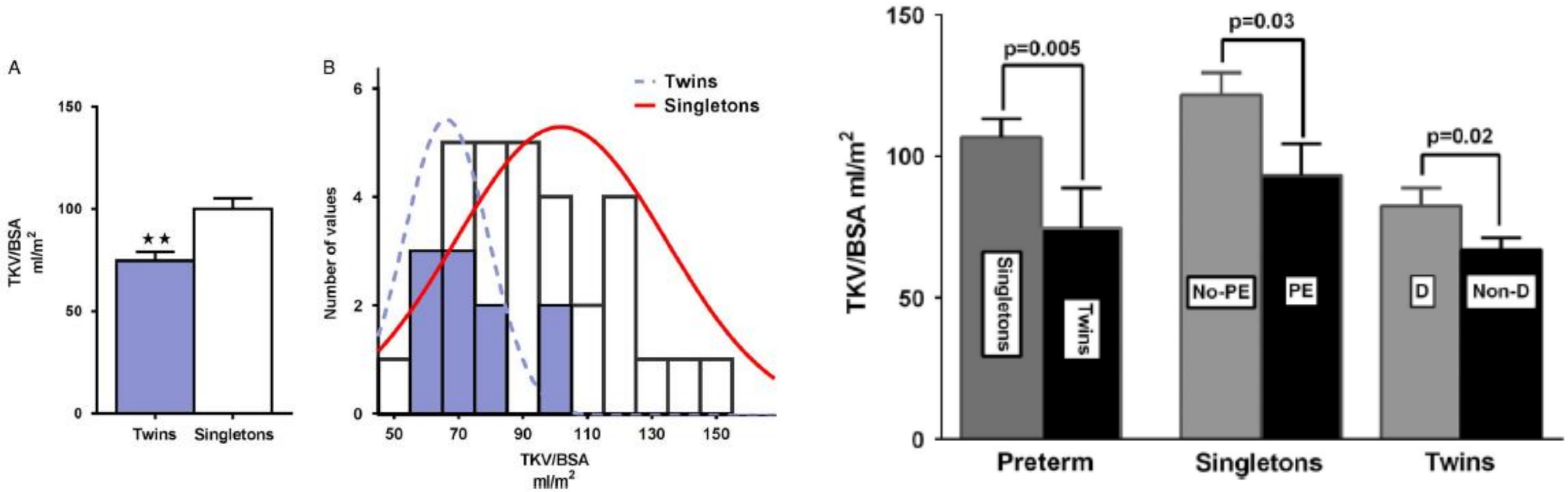


M. J. DeFreitas[1]*, D. Mathur[2], W. Seeherunvong[1], T. Cano[1], C. P. Katsoufis[1], S. Duara[3], S. Yasin[4], G. Zilleruelo[1], M. M. Rodriguez[2] and C. L. Abitbol[1]

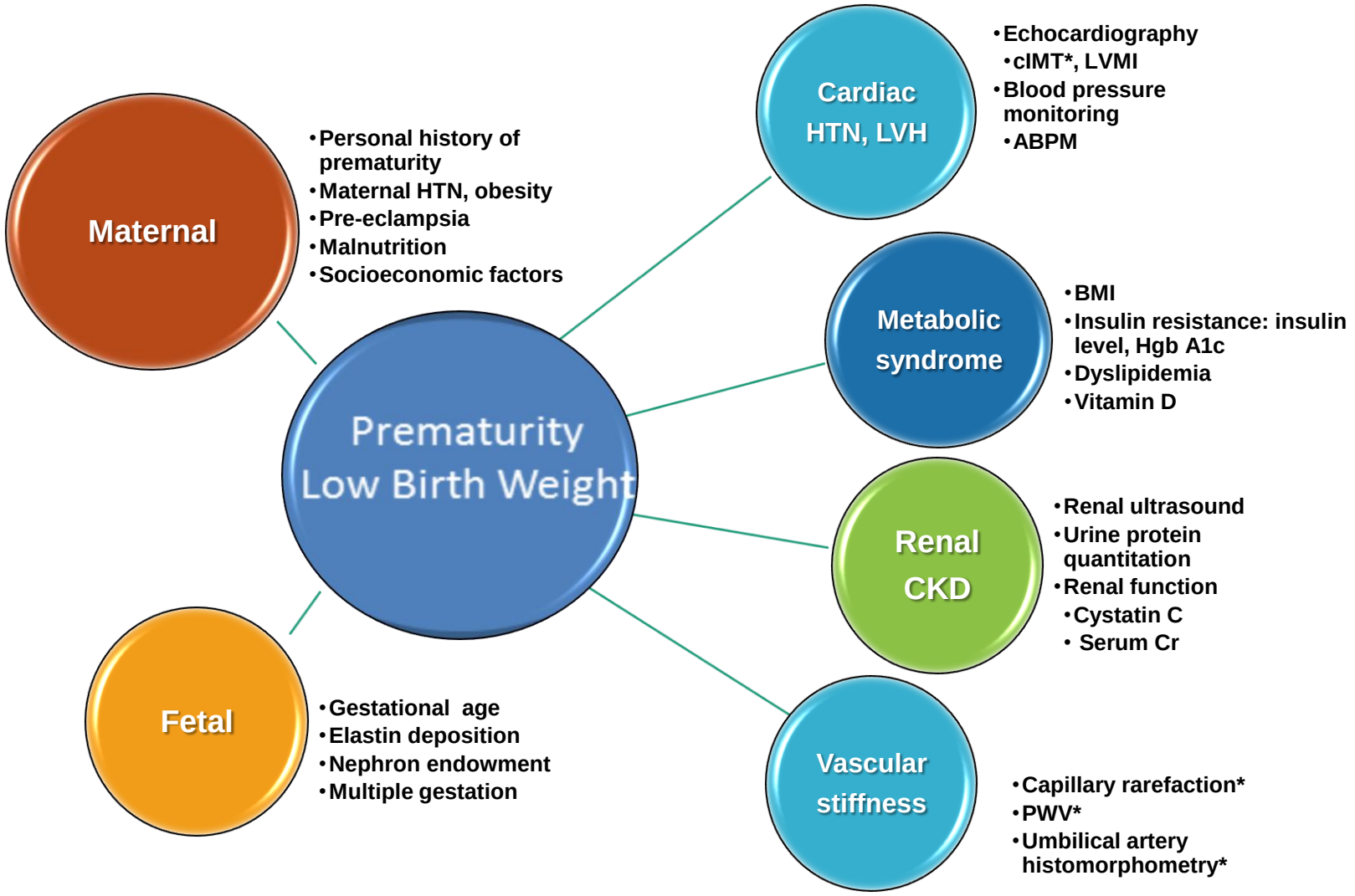
Journal of Developmental Origins of Health and Disease, page 1 of 8.





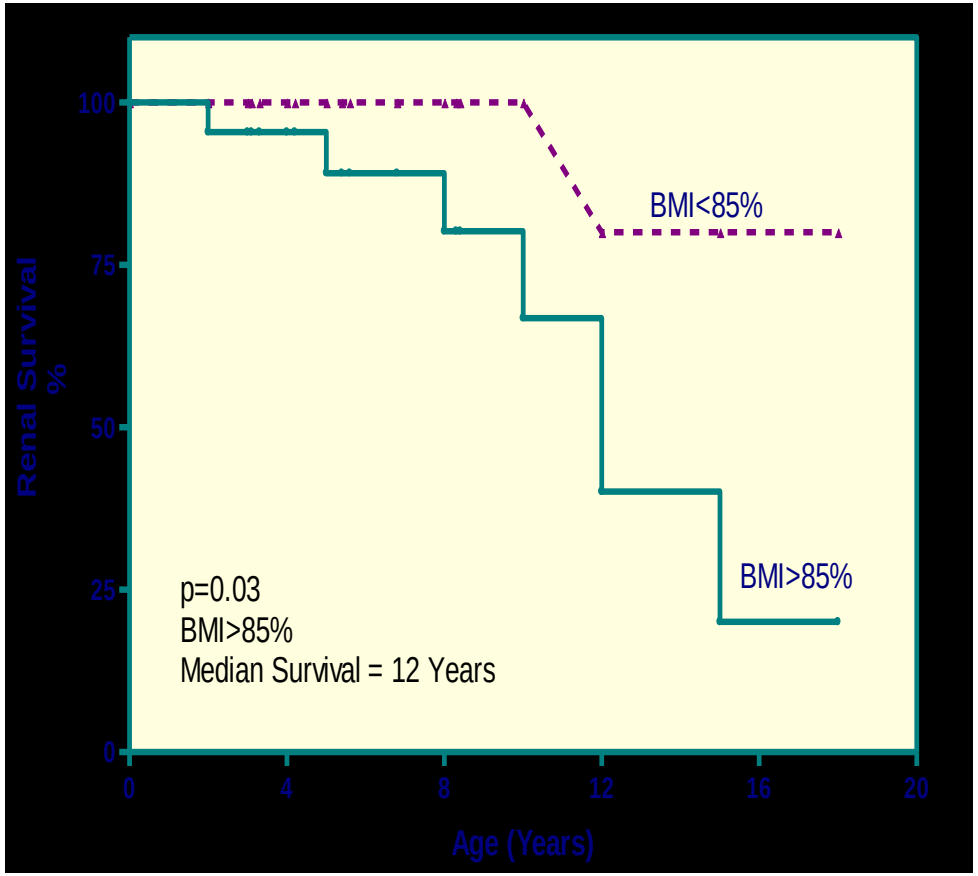

A
150
100
50
0
TKV/BSA
ml/m2
★★
Twins
Singletons
B
6
4
2
0
Number of values
Twins
Singletons
50
70
90
110
130
150
TKV/BSA
ml/m2
150
100
50
0
TKV/BSA ml/m2
p=0.005
p=0.03
p=0.02
Singletons
Twins
No-PE
PE
D
Non-D
Preterm
Singletons
Twins

Comprehensive evaluation schema of the preterm/LBW infant for early cardiovascular and renal disease risks

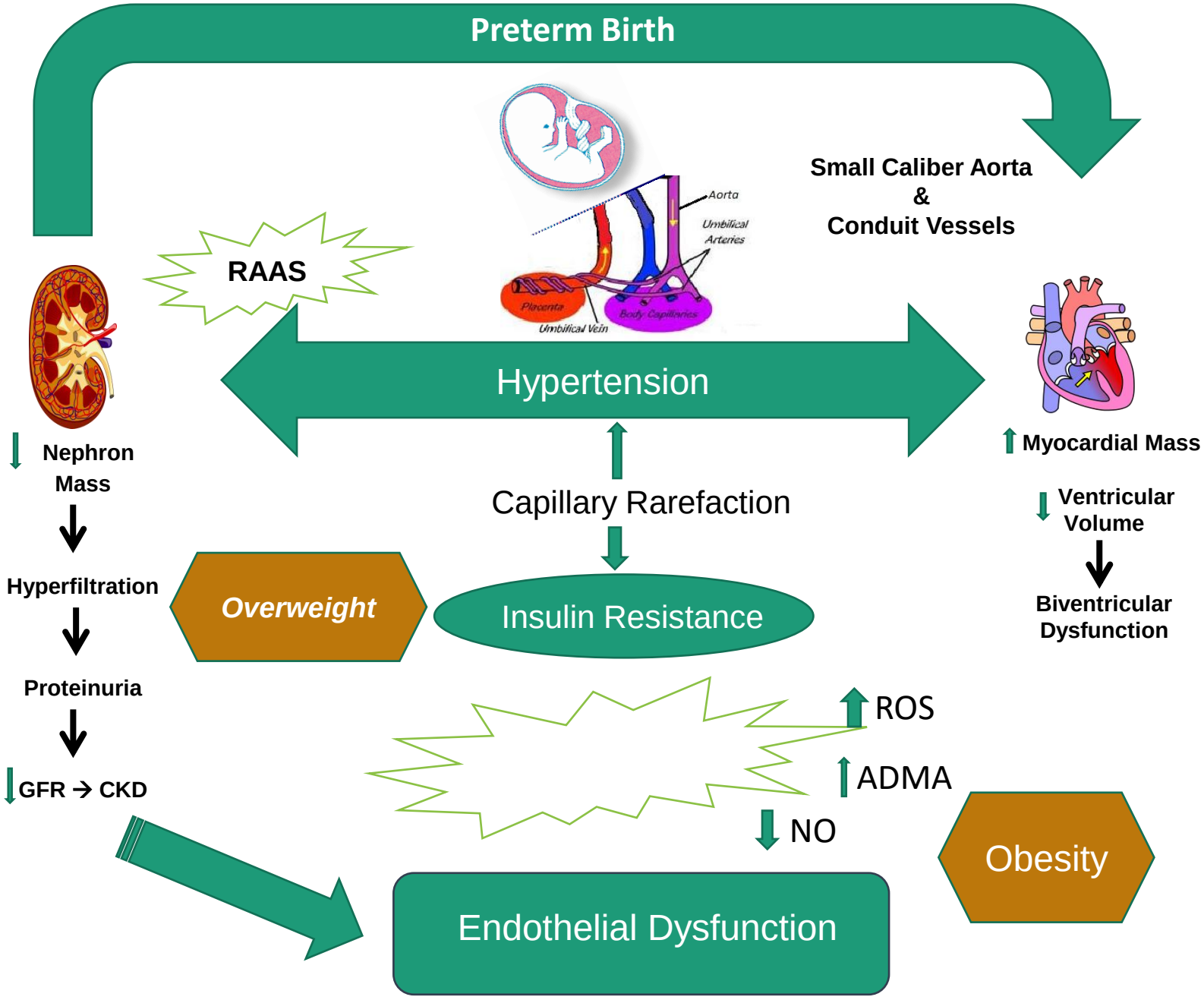


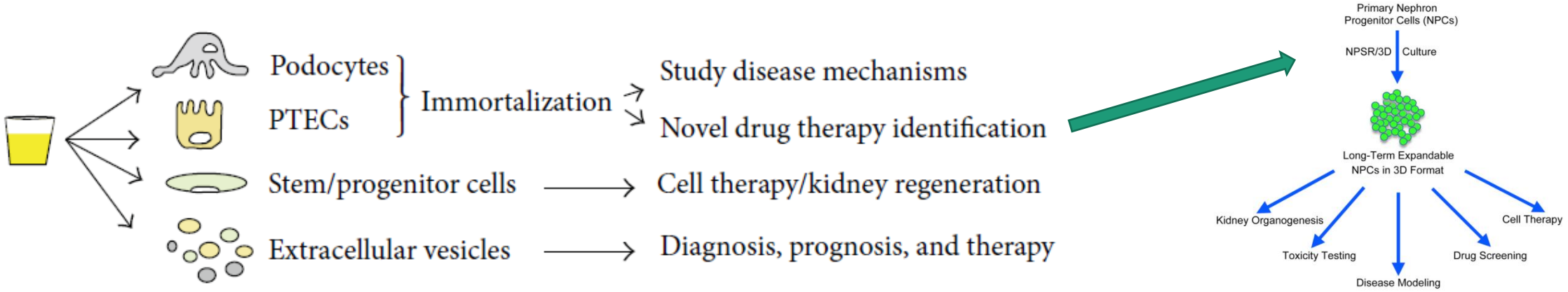
ELBW & BMI:
Components of Renal Disease Progression

- ***Extreme Low Birth Weight*** infants show renal disease progression with increased BMI.



Abitbol et.al. Pediatr Nephr (2003) 18:887-893


Preterm Birth
Small Caliber Aorta
&
Conduit Vessels
Aorta
Umbilical Arteries
Placenta
Body Capillaries
Umbilical Vein
RAAS
Hypertension
Nephron Mass
Myocardial Mass
Capillary Rarefaction
Ventricular Volume
Hyperfiltration
Overweight
Insulin Resistance
Biventricular Dysfunction
Proteinuria
ROS
ADMA
GFR → CKD
NO
Obesity
Endothelial Dysfunction



Urine derived kidney cells	Markers of Disease Activity	Pathophysiology	Therapeutic Potential
Podocytes	Diabetic Nephropathy Pre-eclampsia FSGS & APOL1	Lupus nephritis APOL1	Not yet studied
Proximal Tubular Epithelial Cells	Acute tubular necrosis Diabetes mellitus	Cystinosis Diabetic nephropathy Oxalosis Lowe's Syndrome	
Stem/Progenitor Cells	Not yet studied	Nephrogenesis	Regeneration and repair
Extracellular Vesicles	Focal segmental glomerulosclerosis	Not yet studies	Repair & kidney transplantation

Growing Collaborations: Building Networks of Translational Science Across Disciplines


















BATCHELOR CHILDREN'S RESEARCH INSTITUTE

IPNA

GREAT CARE FOR LITTLE KIDNEYS, EVERYWHERE

JAMAICA KIDNEY KIDS FOUNDATION