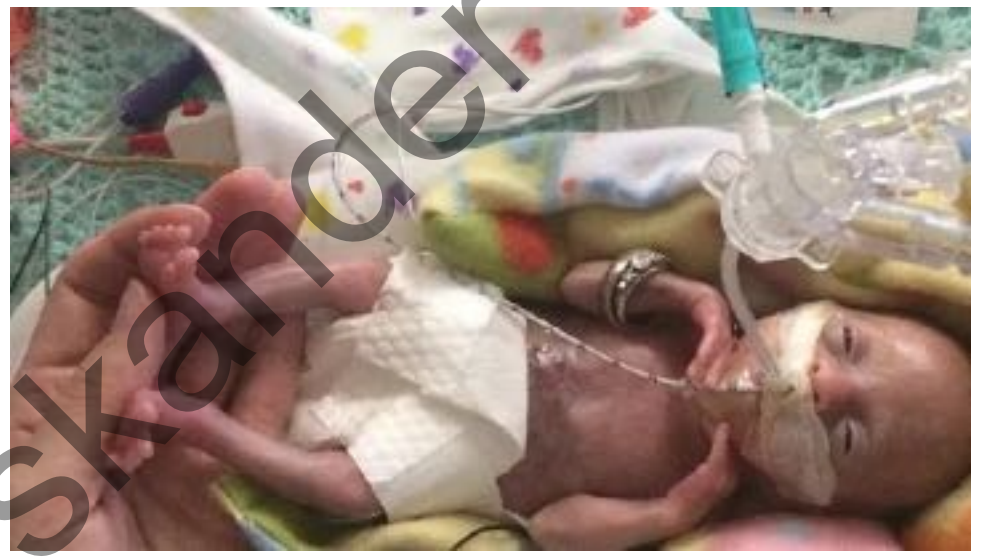
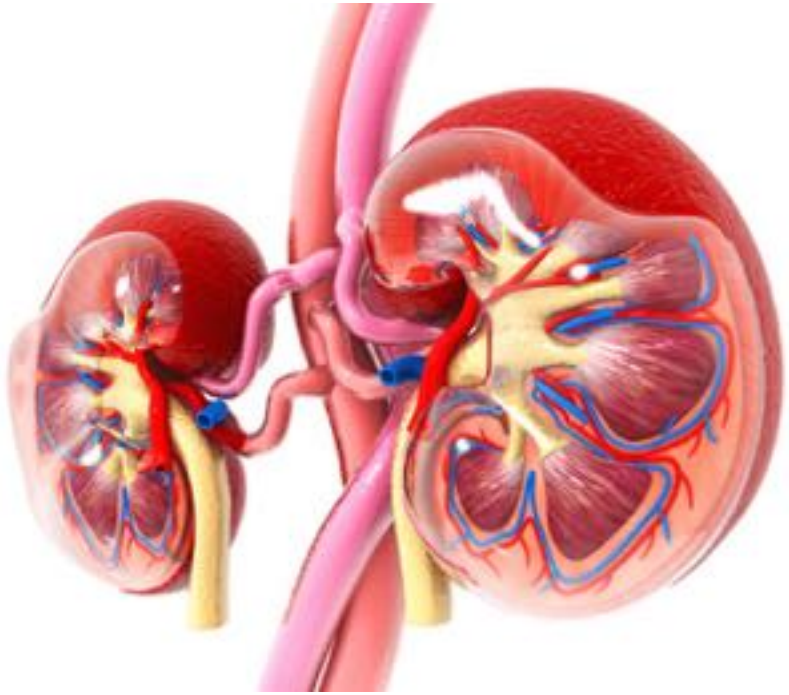
Renal Consequences of Preterm Birth

Iman Iskander MD
Cairo University

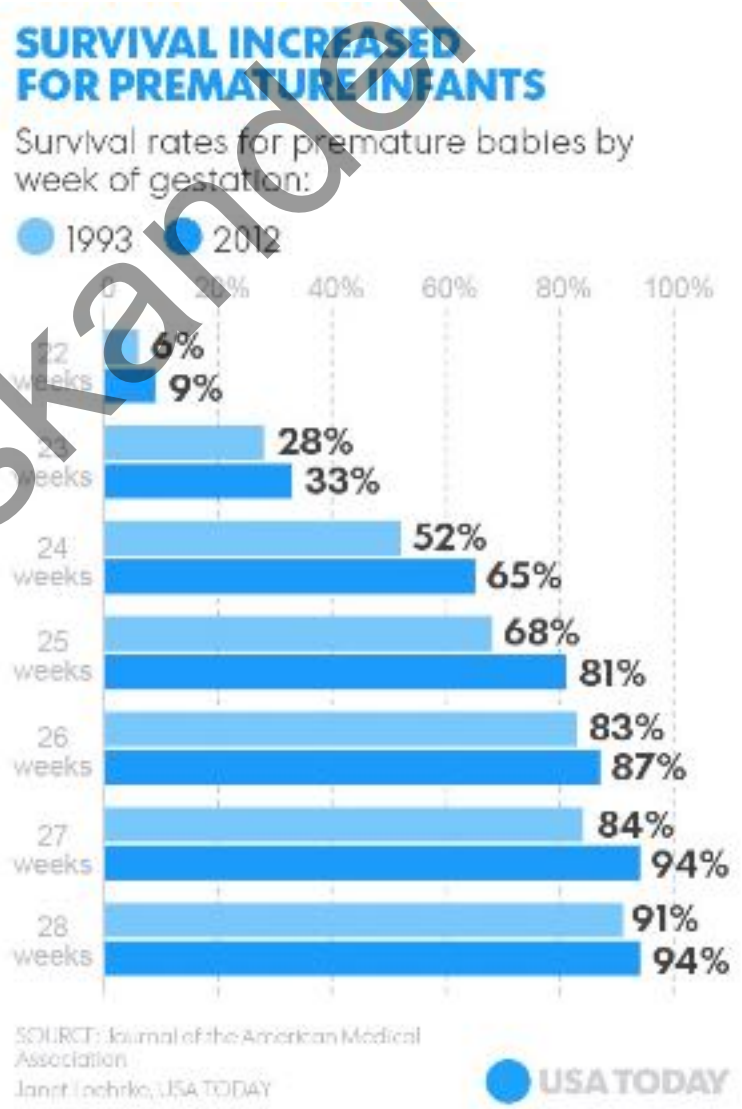




Incidence of Prematurity

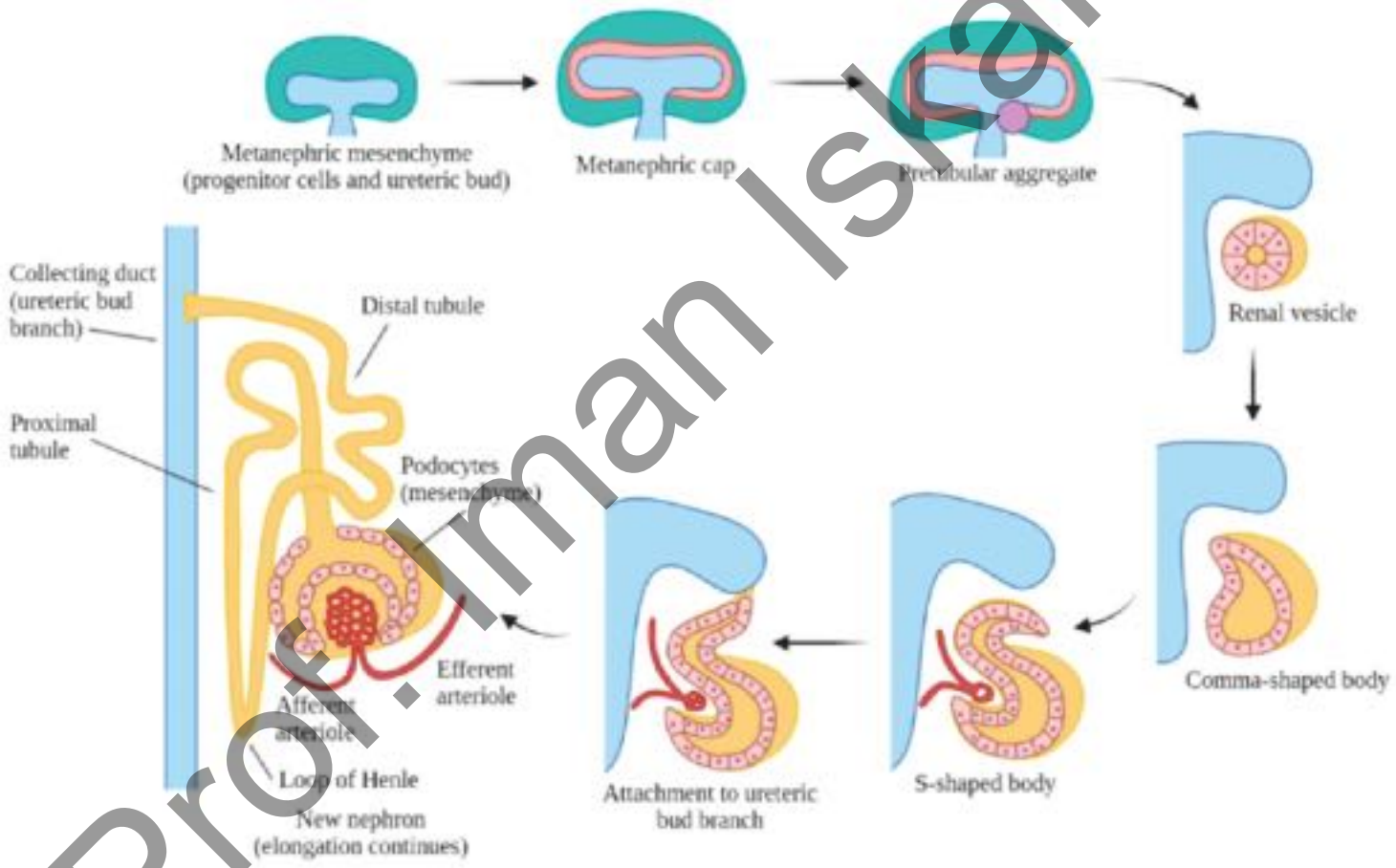
- An estimated 13.4 million babies were born preterm in 2020 (< 37 completed weeks of gestation) .
- Across countries, the rate of preterm birth ranged from 4–16% of babies

(Ohuma et al, 2023)



Normal renal development

Normal renal development (week 5 onwards..



Urine by 10 weeks

Amniotic fluid 16 weeks

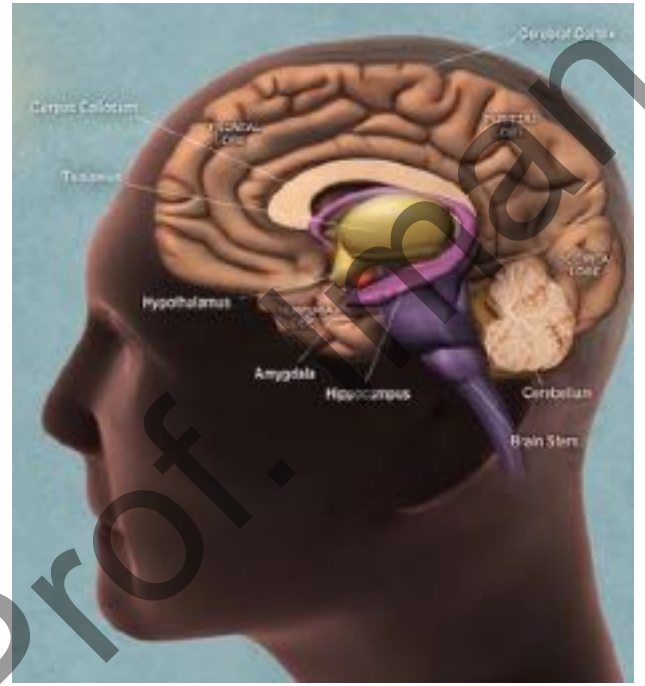
Fetal kidneys grow by branching morphogenesis

Nephrogenesis

- Around 300,000 to > one million nephrons are present at birth
- 4-8 fold variation in nephron number due to : genetic and environmental factors affecting nephrogenesis, and renal insults over time
- Nephronogenesis continues till 34–36 weeks of gestation with more than 60% of nephrons being formed in the last trimester of pregnancy
- Placental insufficiency and IUGR: cerebral redistribution and diversion of blood from less vital organs (impair kidney growth)

Significance of adequate renal function

- *The kidney is important!*
  - MAINTAINS acid base status, electrolyte hemostasis and conservation of micro and macroelements
  - ESSENTIAL for protein accretion, growth and neurodevelopment
- In the NICU optimizing cardiorespiratory function takes precedence over everything to improve mortality.
- The current aim of the NICU is changing: *not only to allow mere survival but to provide a good quality of life for the surviving preterm baby*



Prematurity and the kidney

- Conditions that lead to preterm birth, premature birth itself, and the post natal management of the PT lead to permanent change of organ function and structure.
- Survivors of prematurity are at increased risk of metabolic disease and chronic renal dysfunction
- Systematic review of over 2 million former LBW infants concludes an odds ratio of 1.73 to develop chronic renal disease *(White et al, 2009)*
- Red flag: delay in onset and painlessness of renal disease

Factors affecting the kidney in the IUE

- Maternal diet and nutrition influence nephrogenesis (macro and micro nutrients)
- Maternal smoking :
  - Increases the risk of preterm birth
  - Causes VC and placental insufficiency
  - Smaller kidney size in both fetuses and newborn and later in school children

Maternal medication during pregnancy

- Atosiban OTR blocker, tocolytic , reduce nephron number, block vasodilation effect , Na retention and hypertension
- Steroids reduce nephrogenesis
- Antibiotics (in particular aminoglycosides)cross the placenta and may affect fetal renal function
- NSAID: Indomethacin: AVOID IF POSSIBLE
  - reduce amniotic fluid volume as a result of fetal renal dysfunction.
  - causes glomerular injury and reduce glomerular number in adulthood,

Nephrogenesis in the PT

Maximal human kidney growth occurs between 26 and 34 weeks' GA, with nephrogenesis complete by term GA.

Altered renal development in the preterm

- Most PT are born while still undergoing nephrogenesis
- Glomerulogenesis: arrest by 40 days of birth (histopathologically: slow continuous abnormal glomeruli formation)
- To ameliorate oligonephronia: Activation of the RA system which leads to increase GFR and hyperfiltration (predisposes to genetic hypertension, vascular dysfunction, vessel rigidity, and further constriction)

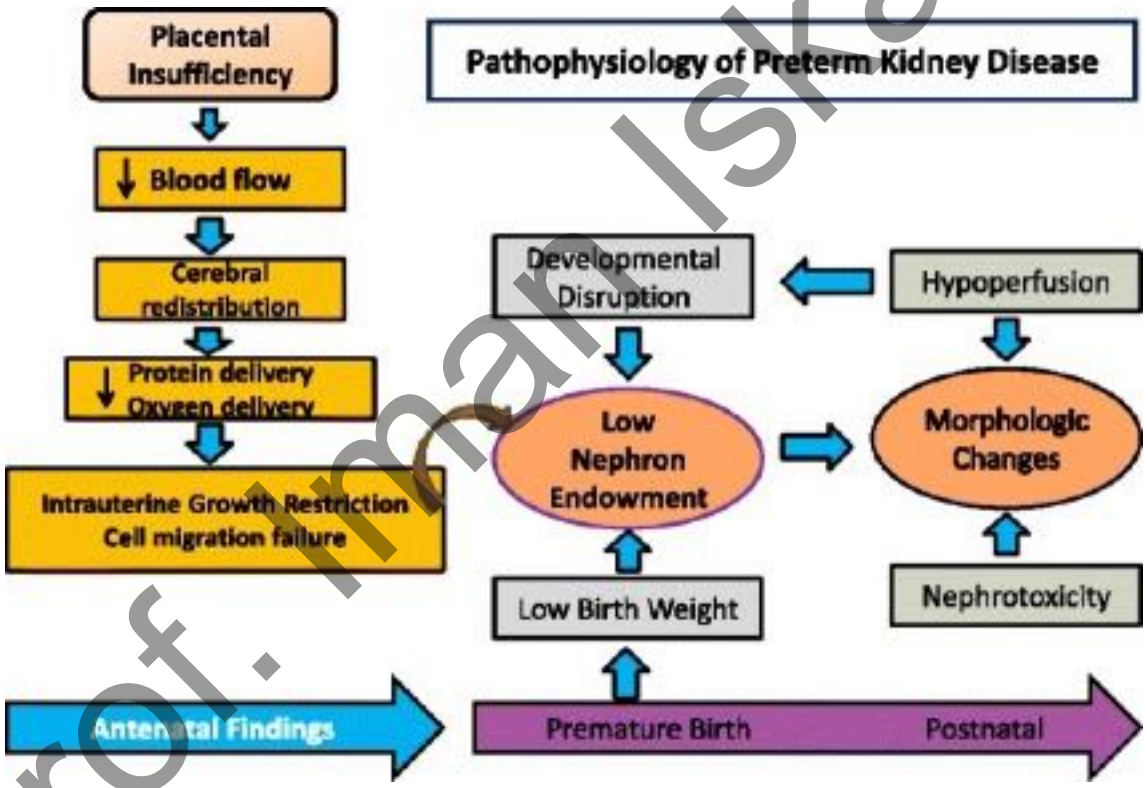
Mechanism of renal affection in LBW baby

- PT AGA: result of an interruption in normal organ and vascular growth followed by ex utero nephrogenesis altered by the postnatal environment.
- SGA FT: pregnancy complicated by placental insufficiency, the fetal kidneys may not have received adequate nutrition or oxygenation for nephron development.

Mechanism of renal affection in PT birth

- Impaired organogenesis due to inflammation or by placental insufficiency, resulting in cerebral redistribution and diversion of blood from less vital organs
- Premature birth
  - Reduction of nephron endowment with lowering GA.
  - Disruption of organogenesis and arrest in branching organs (lungs, vascular tree, and kidney)
  - Microstructural changes: simplification, fibroproliferation, and rarefied, dysmorphic capillaries

Abnormal kidney development in the LBW



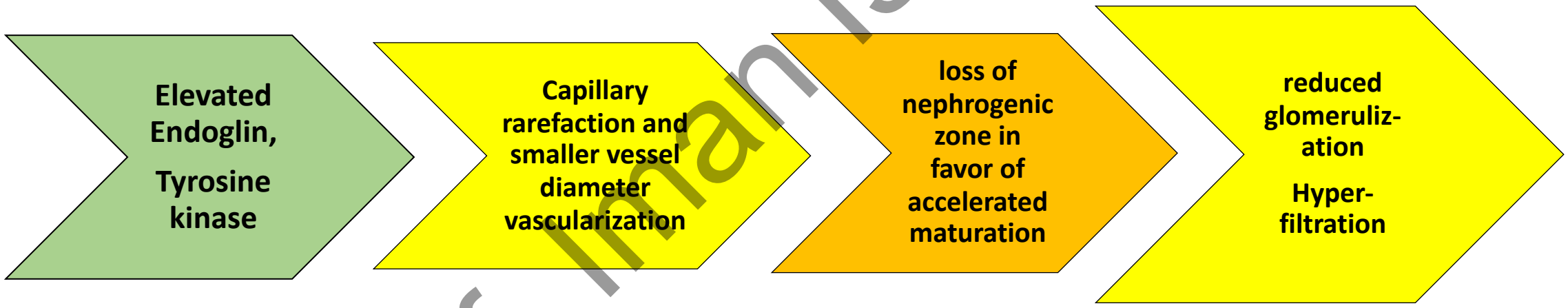
Pathophysiology of renal affection in PT birth

- Poor antenatal perfusion with lack of oxygen and nutrition (protein and micronutrients) impact nephron numbers
- Key molecular influences:
  - Inflammatory cytokines
  - Reactive oxygen species (exposure to hyperoxic environment, medication , xray,)
  - Antiangiogenic factors (reduced vascular endothelial growth factor (VEGF) signalling)

Reactive oxygen species:

- Due to:
  - Relative hyperoxia after delivery compared to fetal oxygen tension
  - Exposure to oxygen radicals (TPN, and X-rays)
- Effect of relative hyperoxia
  - Vessel paucity: arrested proliferation and increase apoptosis secondary to:
    - Increased hypoxia-induced-factor 1 (HIF-1),
    - reduced vascular endothelial growth factor (VEGF) signaling
    - Susceptibility of neonatal endothelial progenitor cells (EPC)
  - Vessel constriction due to impaired endothelium-mediated vasodilation
  - 25% reduction in nephron numbers in mice persisted till adulthood

Antiangiogenic factors



Post natal environment and the kidney

What happens following birth?

- Increase perfusion pressure of fetal kidney from 3% to 15% of the cardiac output by 6 weeks of life
- Sudden decrease in glomerular vascular resistance with doubling of GFR within days
- The arterial oxygen tension increases suddenly after preterm birth, altering the environment in which organogenesis occurs.
- Hyperoxia and hypoxia are both deleterious to the outcomes of preterm infants and both should be avoided in the NICU

Exposure to potential nephrotoxic drugs in the NICU

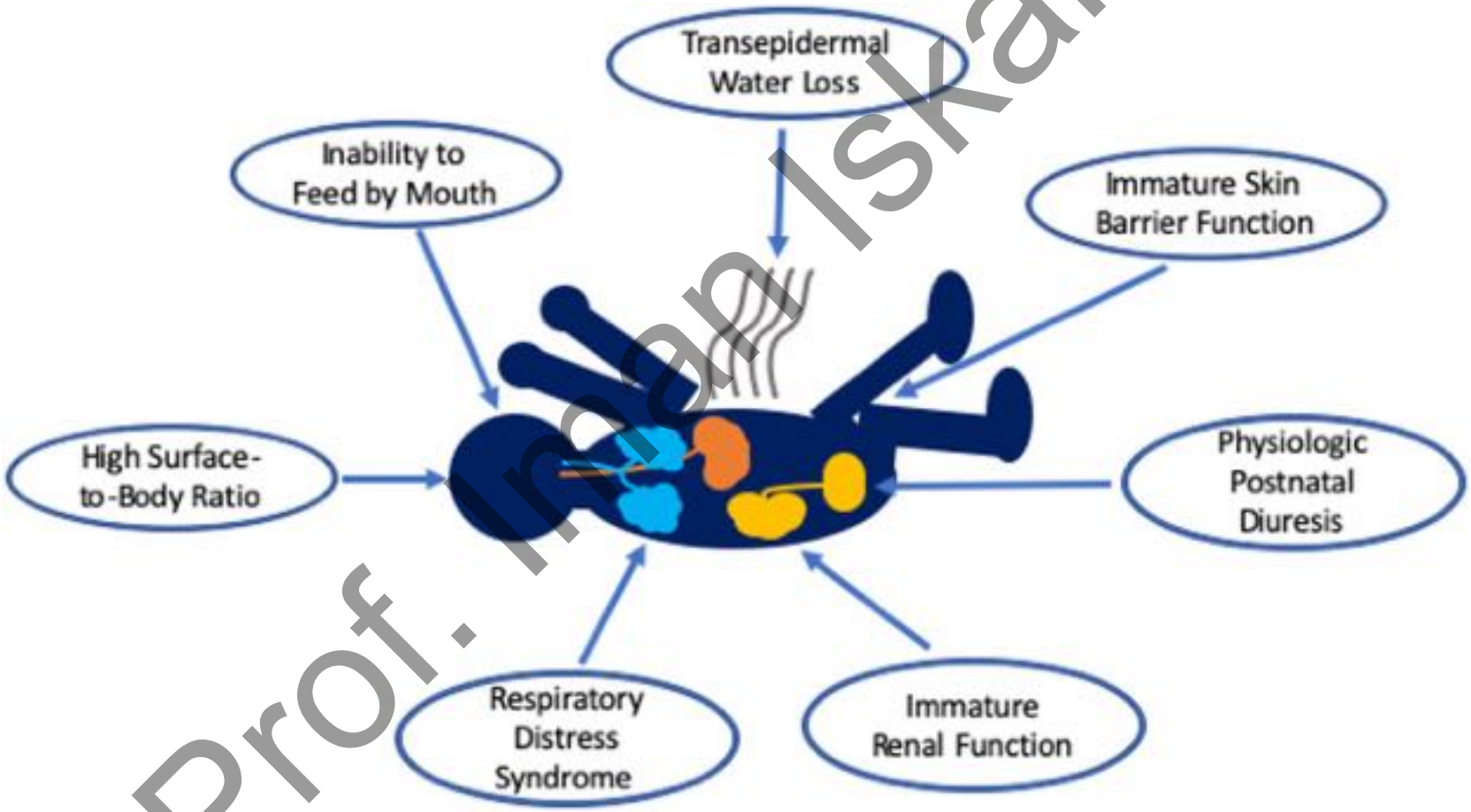
It has been shown that up to 87% of VLBW infants in NICUs are exposed to more than 1 nephrotoxic medication

- antibiotics
- non-steroidal anti-inflammatory drugs (NSAIDs)
- angiotensin-converting enzyme (ACE) inhibitors
- Steroids

Renal insults common in the preterm

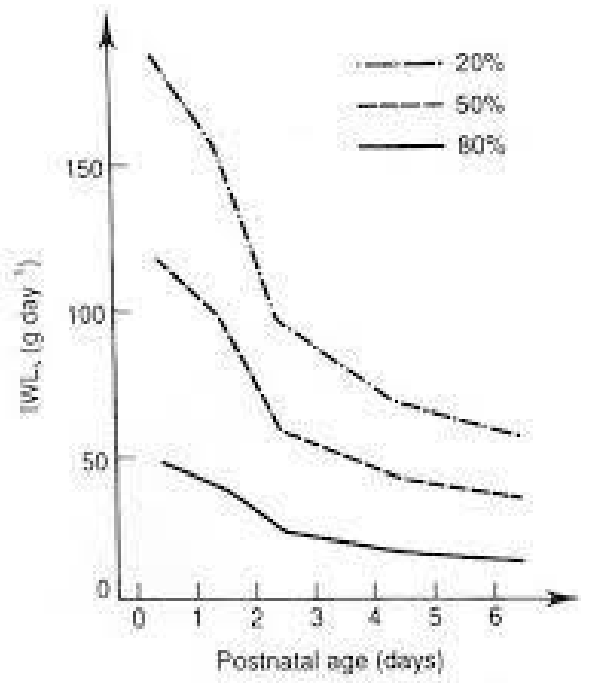
- Hypoperfusion: Asphyxia, blood loss or PDA cause cardiovascular decompensation and hypotension
- In the absence of healthy regulation of blood flow via dilatation of the afferent vessels by prostaglandins and vasoconstriction of both efferent and afferent renal vessels by angiotensin result in oliguria
- Difficult fluid balance

Fluid balance in the preterm: Very Difficult!

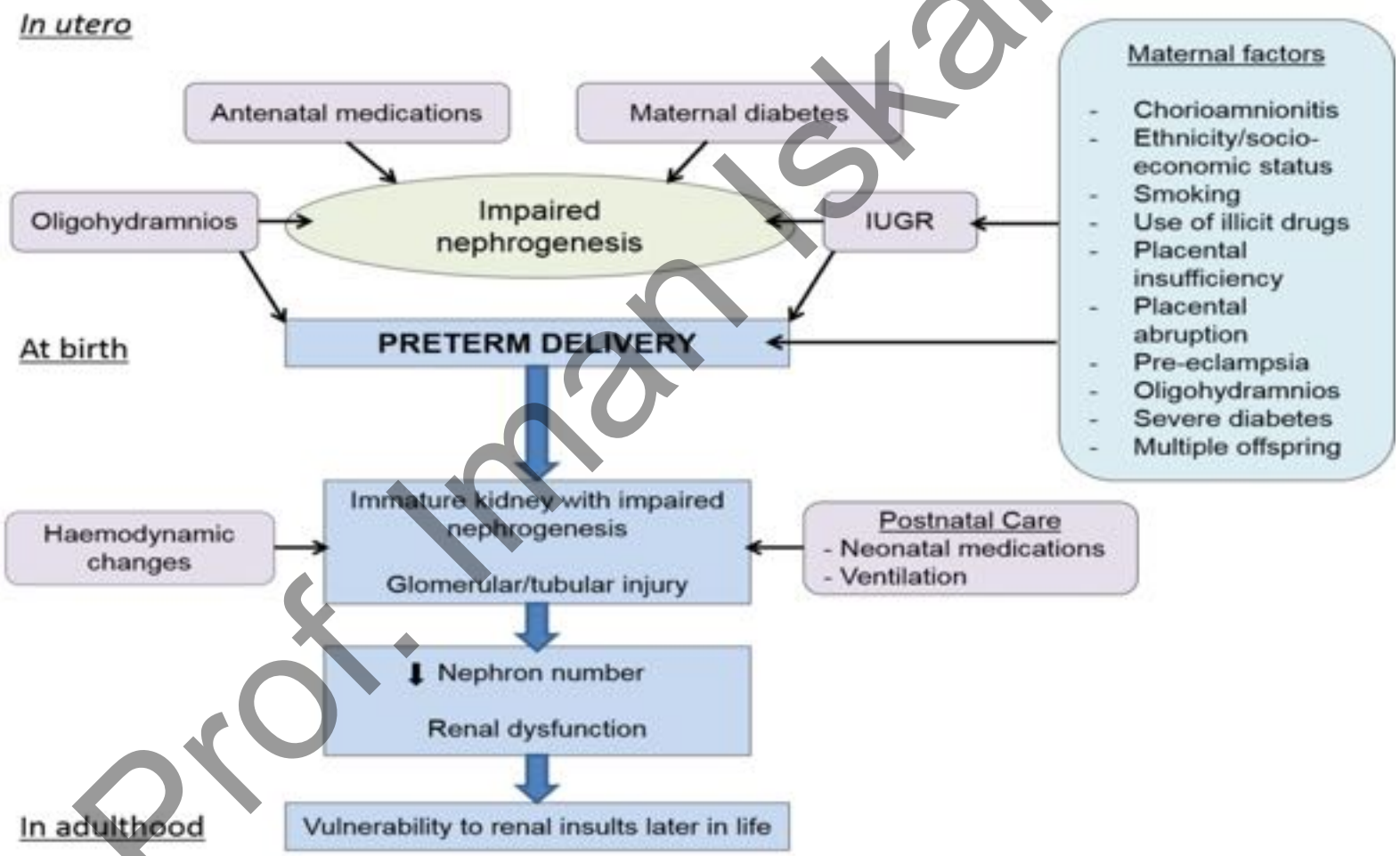


Proper fluid balance (*Branagan et al, 2022*)

- Aim: Euvolemia
- Insensible losses (substantial in ELBW): Increases with decreased GA and BW. Humidification reduces ISL.
- Fluid resuscitation: restore circulating volume and optimize renal perfusion in hypovolemia.
- Close monitoring of the response to fluid challenge (10–20 ml/kg over 1–2 h) to avoid fluid overload as is associated with poorer outcomes



The risks for the preterm kidney



Problems of the preterm kidney

- Impaired ability to conserve water and concentrate urine in renal hypoperfusion states
- Leaky tubules: (*tubulopathy of prematurity) mostly transient:*
  - It describes a condition of renal immaturity with limited responsiveness to aldosterone: kidneys are unable to adequately handle free water, electrolytes, small proteins, and bicarbonate
  - Loss of bicarbonate, electrolytes, and small proteins may lead to metabolic acidosis, electrolyte imbalance, and poor growth.

Problems of the preterm kidney

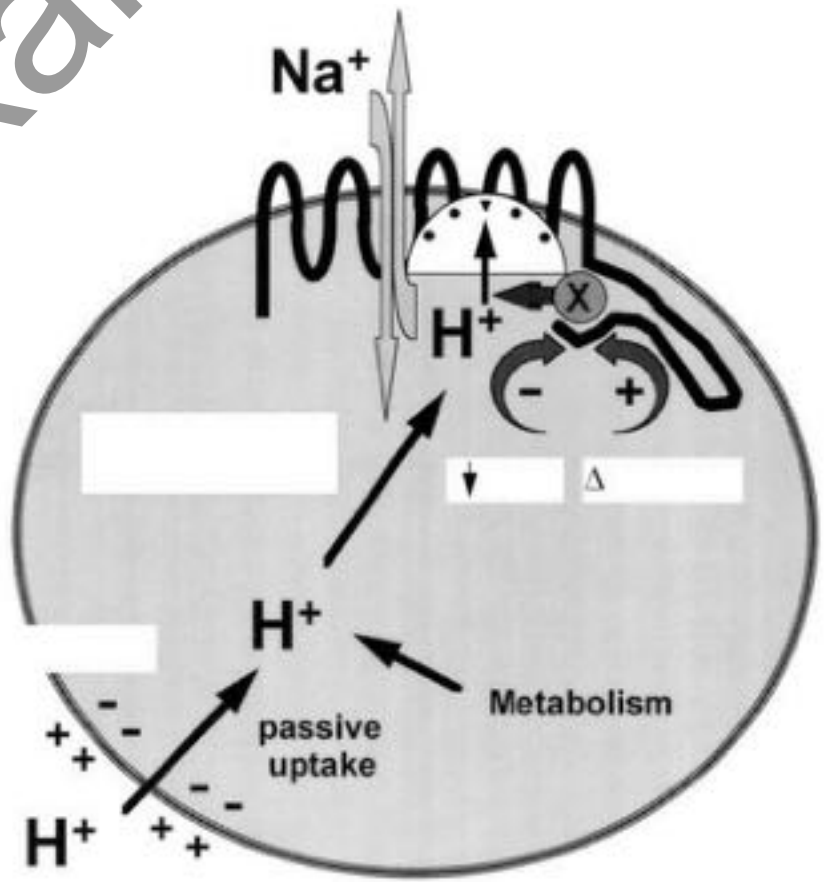
- Acidosis
  - Mild metabolic acidosis, i.e., base excess less than minus 4 or bicarbonate less than 18 mmol/l, **remains a concern in up to 30% of neonates** with tubulopathy of prematurity and with use of human milk fortifiers
  - High acid load and age-related low renal capacity to excrete acid exhibits impaired growth and reduced bone mineral content in the stable premature

Problems of the preterm kidney

- Hyponatremia : 25% of infants with GA < 33 weeks
  - Na Supplementation (3–5 mmol/kg/day) is generally commenced after physiologic weight loss is attained
  - Recommended supplementation aimed to maintain normal serum sodium(135–145 mmol/l) often fails and additional doses are required
  - Decision for Na supplementation is difficult: serum sodium concentration may be lagging total body sodium depletion and its value is inevitably affected by hydration status

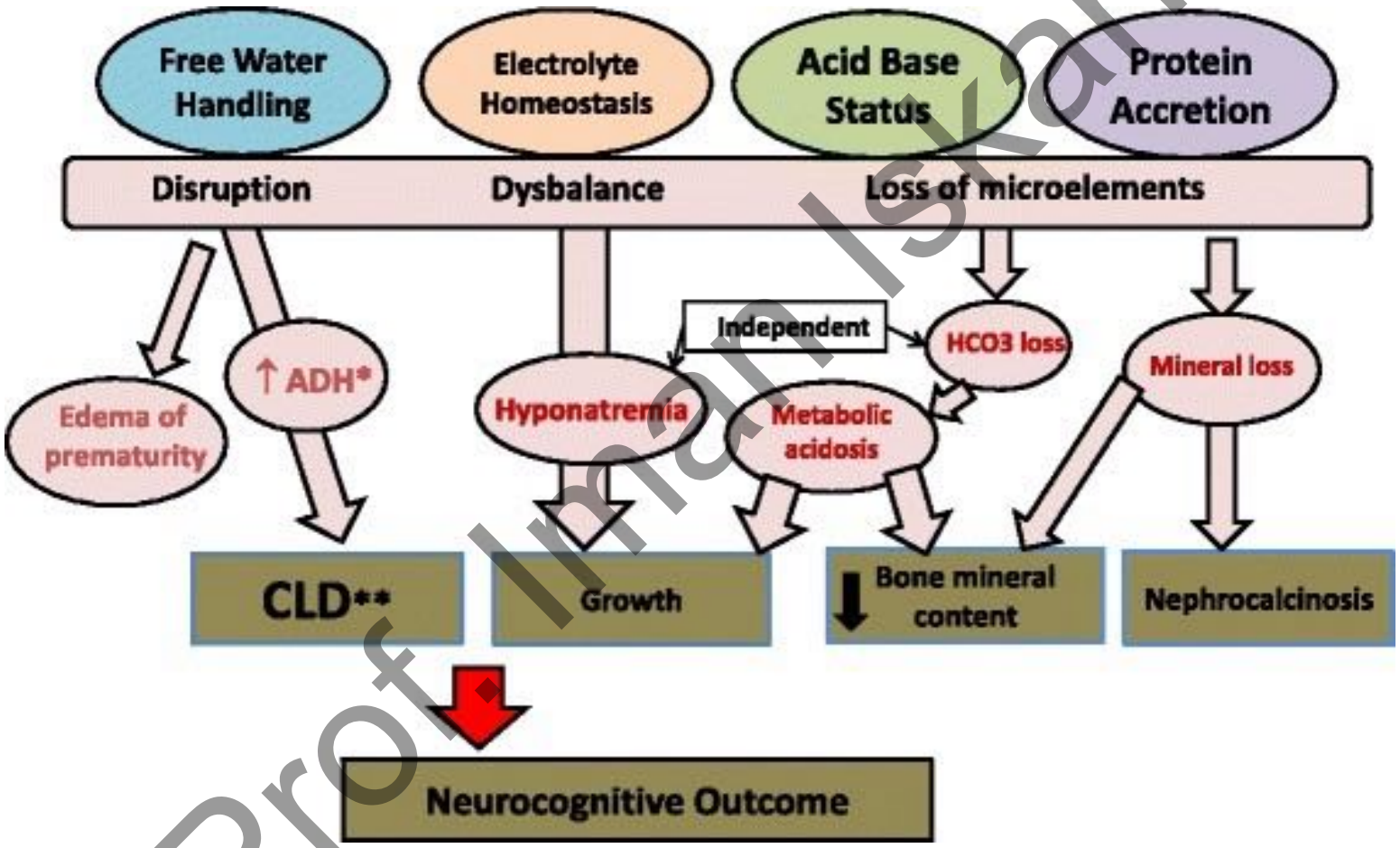
Problems of the preterm kidney

- Growth:15 gm/kg/ day lean tissue requires net sodium storage of 1–1.5 mmol/kg/day
- Na dependent **Na/H antiporter system** in the cell wall which increases Na/K ATPase and stimulates growth by alkalinization of the cell interior.
- Low Sodium and acidosis reduce the activity of this antiporter: growth failure despite adequate macronutrient intake , affects neurodevelopmental outcome
- Poor weight gain despite adequate nutritional intake: marker of tubulopathy



Problems of the preterm kidney

- Nephrocalcinosis
  - Occurs in 14% of PT< 34 weeks
  - Associated with decreasing birthweight, increased calcium, phosphorus, and ascorbic acid intake; exposure to furosemide, dexamethasone, thiazides, and theophylline (Lee et al, 2014).
  - Kist-van Holthe et al (2007): former PT <32 weeks' GA with nephrocalcinosis ; more likely to have mild renal insufficiency and tubular dysfunction compared with control subjects at age of 7.5 years
  - May predispose to long term renal dysfunction



Long Term Renal Consequences of Preterm Birth

Kidney size and function

- Smaller kidneys at term at 7-11 years (Starzek et al, 2016) they might have larger kidney-to-bodyweight ratios because of glomerular hypertrophy.
- Post natal catch up growth in kidney size is not necessarily associated with normal renal development (Li et al, 2019)
- Adults born at <29 weeks' GA had smaller kidneys (average age 23 years) compared with matched term-born controls. No difference in e GFR/ Higher albumin creat ratio(endothelial integrity) *(HAPI study,* Paquette et al, 2018)

Dysfunction

- In SGA, hypertension, lower GFRs and salt sensitivity higher in 47% compared to 18% in term peers (Simonetti et al, 2008)
- Microvascular endothelial dysfunction (increased vascular resistance) worsens nephron deficit in the premature kidney
- Low nephron count and reduced capability of the afferent arteriole to adjust incoming pressure → increased glomerular capillary pressure (glomerular hypertrophy, hyperfiltration, proteinuria via activation of RAS, and glomerulosclerosis)

Prematurity and CKD

- CKD is a growing public health problem contributing to global mortality.
- The renal consequences of preterm birth:
  - higher risk of chronic kidney disease (CKD),
  - a quicker progression of renal pathology,
  - predisposition toward hypertension.
- Increased survival of preterm population further increase CKD

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]

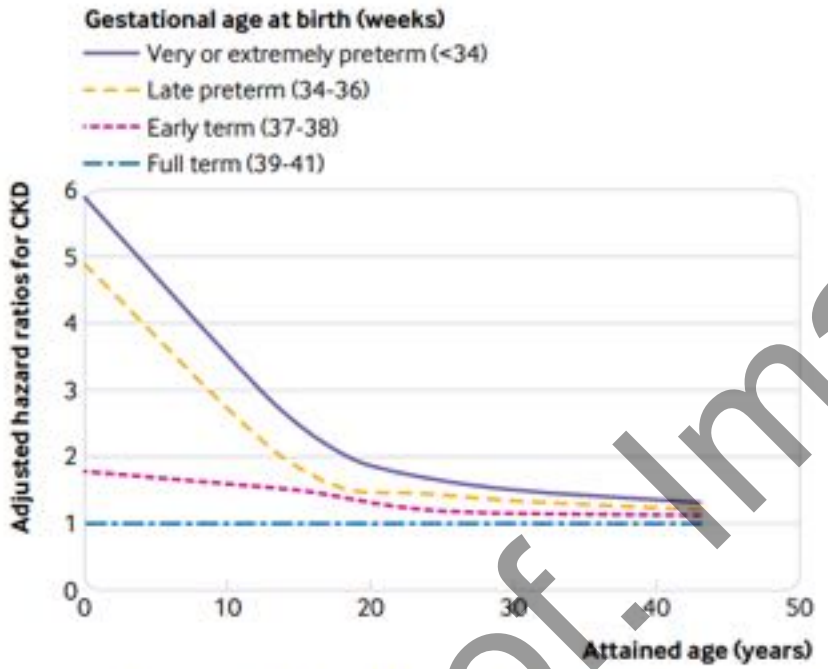


Fig 1 | Adjusted hazard ratios for chronic kidney disease (CKD) by gestational age at birth compared with full term birth, Sweden, 1973-2015

- 4,186,615 singleton birth (1974-2014) in Sweden
- Incidence rates CKD : 9.24% for preterm infants, 5.9 % for early term, and 4.47 % for full term
- Neonatal ARF was identified in 300 participants (83 preterm), of whom 72 developed subsequent CKD (15 PT).

Crump et al, BMJ 2019

Risk factors for CKD in the preterm

- Preterm have increased risks of CKD extending into mid-adulthood. (The incidence of CRF is inversely proportional to GA and same in both sexes).
- SGA babies are also at increased risk
- Early term birth associated with increase risk of CRF (from childhood into adulthood) showing that decreased nephron endowment is not the only cause of renal impairment
- Other risk factors for CKD : male sex, congenital anomalies, and maternal obesity, maternal preeclampsia, post natal environment!

Is there anything we can do?

Renal conservative strategies

- Start right after delivery and continue throughout NICU stay and long-term follow-up.
- Monitoring markers of kidney function such as creatinine, electrolyte, fluid, weight, and acid-base status, careful attention to type and amount of intake
- Choose kidney friendly medicines where possible, as well as monitoring drug levels of renally excreted drugs and reducing prescribed amounts adequately.
- The use of diuretics in oliguria may be a double-edged sword as the increase in urinary output is often offset by an increase in creatinine

Renal conservative strategies

- Nephrotoxic administration: only controllable risk factor for AKI: (NINJA project) the Nephrotoxin Injury Negated by Just-in-time Action to reduce AKI
- Daily creatinine measures in noncritically ill children who are either receiving 3 simultaneous nephrotoxins or have received an aminoglycoside for more than 3 days has been shown to reduce AKI by 68%.Trials of this approach need to be conducted in neonatal populations.

Renal conservative strategies

- Meticulous attention to nutritional support and supplementation with bicarbonate, sodium, phosphate, and other micronutrients in neonates with increased tubular losses may be beneficial.
- Avoidance of edema and fluid overload with renal replacement therapy.
- Renal replacement therapy can be considered in refractory acidosis, uremia, electrolyte imbalance, nutritional deficits, and especially fluid overload .
- Peritoneal dialysis is the method of choice in the preterm (the availability of continuous renal replacement therapy systems designed for the neonate which accommodate smaller extracorporeal volumes and higher accuracy is essential)

Renal conservative strategies

- Long-term strategies include:
  - Monitoring for hypertension with appropriate workup and choice of medication
  - Monitoring for nephrocalcinosis
  - Health education regarding lifestyle choices that are likely to later worsen kidney condition

الخلاصة

TABLE. **Summary of the Effects of Preterm Birth on Renal Health Outcome**

	RISK FACTOR	RENAL HEALTH OUTCOME
Antenatal period	Maternal malnutrition	Poor renal growth (44)
	Maternal smoking	Increased risk of preterm birth (45) Smaller kidney volume and eGFR at school age (46)(47) Proteinuria at 3 years of age (48)
	Maternal alcohol consumption	Mild CKD in offspring in their 30s (39)
Perinatal period	Low birthweight	Increased risk of end-stage renal failure (36)(37) Increased risk of chronic kidney disease (19)(38)(39) More rapid decline in kidney function when there is underlying kidney disease (21)
	Ex utero nephrogenesis	Abnormal glomerulogenesis (26)(40)
	Acute kidney injury	Reduced nephron mass (14) Mortality (70)
	Postnatal growth failure in very-low-birthweight infants	Reduced GFR relative to term controls (78)

Dyson and Kent, Neoreviews 2019

Childhood and adulthood	Preterm birth	Renal size and function	Smaller kidney size relative to term born controls (6)(86) Larger kidney to bodyweight ratio relative to term born controls (13)(14)(15)
		Renal function	Increased risk of nephrocalcinosis (81)(82) Higher albumin to creatinine ratios than term born controls in young adulthood (6) Reduced eGFR relative to term born controls at 7-11 years of age (87)(88) Increased risk of chronic kidney disease persisting into mid-adulthood (4)
		Hypertension	Alterations in the function of the renin-angiotensin system (6)(90)(91) Higher blood pressure than term controls in childhood and adulthood (92)(93)(94)(95) A greater hypertensive effect in former preterm women than men (95)(96) Increased salt sensitivity (ie, blood pressure changes in relation to a high salt diet) (97)
	Nutrition		Obesity is an additive risk factor to prematurity for proteinuric kidney disease (79) Greater risk of insulin resistance (99)

eGFR=estimated glomerular filtration rate; CKD=chronic kidney disease.

Dyson and Kent , Neoreviews, 2019

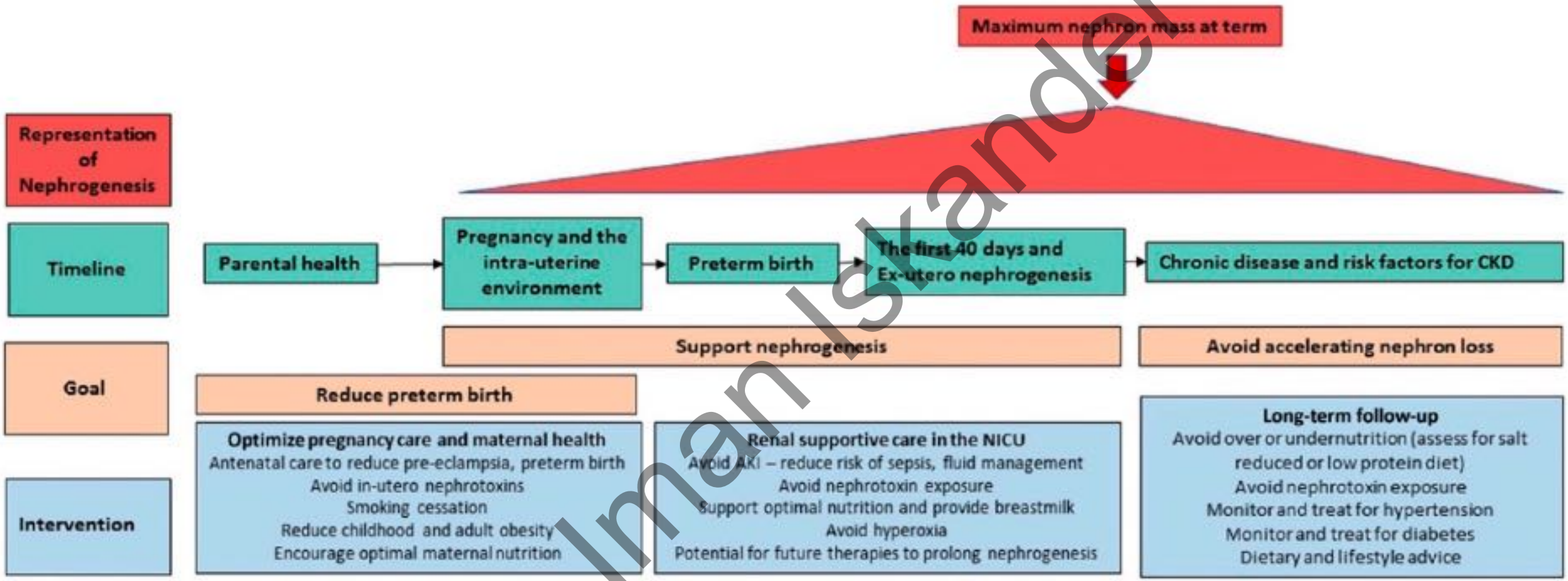


Figure. Timeline of nephrogenesis outlining potential opportunities to support renal development in preterm infants. AKI=acute kidney injury; CKD=chronic kidney disease.

Dyson et al, 2019

Table 2 Proposed practice guidelines for optimization of renal conservation efforts

	During NICU	Health Maintenance for survivors of prematurity
Monitoring renal function	Volume status, weight, ins and out Vital signs Serum electrolytes, crea, and FeNa: Supplementation if prudentMaintain target serum electrolyte values	Awareness of prematurity-related increased risk throughout lifespan [7] Assess serially volume status, weight, diuresis Vital signs (esp BP) Tubular parameters (FeNa/β2-M) Glomerular parameters (albumin/creatinine)
Medications	Drug levels/pharmacist input=> Dosing adjustment Taking renal maturation into account Daily evaluation of medications	Awareness of baseline renal function appropriate choice and adjustment of potential medications
Arterial hypertension	Blood pressure monitoring daily as needed in the acute/sick phase or if abnormal Rule out coarctation aortae Consider renal vascular Doppler	Blood pressure measurement With every health maintenance visit Target age-appropriate values [74] Counseling about salt sensitivity
Nephrocalcinosis	Renal ultrasound before discharge	Follow-up ultrasound for resolution If progression consider urine Ca/creatinine

Crump et al, BMJ 2019

Conclusion

- The toll of prematurity-related renal injury on the probability of kidney disease in adulthood is understudied.
- Survivors of extreme prematurity suffer arrested development with reduced nephron endowment due to hypoxic-ischemic and nephrotoxic renal insults.
- Short-term consequences include electrolyte imbalances, acidosis, and impaired free water handling which could result in prolonged respiratory support, growth failure, and suboptimal neurodevelopmental outcomes in the short term.

Conclusion

- In later life, subclinical chronic renal insufficiency may progress
- For the neonatologist, improving extremely premature infants' outcomes depends on the awareness of renal implications of therapeutic interventions and renal conservation strategies with prudent follow-up.
- Novel markers of AKI, as well as new treatment strategies such as early dialysis can be explored further..

DO NO HARM

AVOID FURTHER CONTRIBUTION TO NEPHRON LOSS

When does nephrogenesis end in the preterm?

A. At birth
B. At 40 days post gestation
C. After 40 days post gestation
D. At 36 weeks
E. Non of the above

Which of the following is related to growth failure in the preterm?

A. Hypercalcemia
B. Hypokalemia
C. Metabolic alkalosis
D. Hyponatremia
E. Hypermagnesemia

Which of the following are risk factors for renal injury in the fetal life?

A. Phenobarbitone
B. Pethidine
C. Oxytocin
D. Vancomycin
E. Steroids