REVIEW ARTICLE

Developmental origins of health and adult disease: What should neonatologists/paediatricians be considering about the long-term health of their patients?

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Abstract: The developmental origins of health and disease hypothesis is now strongly supported by both animal and human evidence, and as a consequence, obstetricians, neonatologists and paediatricians need to consider the impact that the in utero and early post-natal environment can have on later renal, cardiovascular and metabolic health. Four common clinical scenarios were provided along with animal and human evidence identifying long-term health implications. Suggestions as to how we should translate this growing body of evidence into practice are provided.

Key words: cardiovascular; developmental origins; metabolic; neonate; premature.

Since Barker first hypothesised that fetal growth had an influence on long-term cardiovascular outcome, there is now mounting evidence to support the hypothesis.^{1,2} Given this, what should our focus be as neonatologists and paediatricians to ensure that our patients have as healthy a start to life as possible and minimise long-term health risks?

Clinical Scenario 1

Consider a premature male infant born at 26 weeks gestation weighing 880 g (50th percentile) delivered without the benefit of antenatal steroids with evidence of chorioamnionitis and funisitis on placental examination. In the first few days of life, he is noted to have a patent ductus arteriosus (PDA) and is treated with indomethacin for 6 days. He is able to be extubated and commences on oral feeds. On day 10, he deteriorates with increasing apnoeas and bradycardias and evidence of sepsis. He is re-intubated and increasing abdominal distension is noted

with discolouration of the abdominal wall. An abdominal X-ray reveals free gas, and at laparotomy, a jejunostomy is formed for necrotising enterocolitis. He recovers but requires prolonged total parenteral nutrition, and his discharge weight is on the 10th centile with length and head circumference on the third centile. What risk factors are there for long-term cardiovascular/renal consequences?

Much neonatal research has focused on brain and lung injury as they obviously have significant impact on long-term neurodevelopmental outcome and mortality; however, long-term cardiovascular health is now becoming an important consideration. With the developmental origins of health and disease hypothesis gaining momentum, research in both animal and human studies is indicating potential fetal/post-natal programming of renal function. Galinsky *et al.* have shown that in the preterm fetal sheep model, exposure to chorioamnionitis results in reduced nephron number.³ Prenatal glucocorticoid exposure in the fetal sheep model also results in reduced nephron number and hypertension in the adult sheep.^{4,5} However, this animal evidence has not necessarily translated into human findings, with evidence being variable as to antenatal steroid exposure and later hypertension.^{6–9} However, three of these studies were in children/young adults less than 19 years old where hypertension may not yet have occurred. These studies did find differences in systolic blood pressure (BP) and glomerular filtration rates, which may result in later hypertension and renal compromise. Given the overall significant mortality and morbidity benefits of antenatal corticosteroids however, withholding antenatal steroids with the view to reduce potential long-term cardiovascular risk is not an option. Research into ways to mitigate the long-term health risk caused by antenatal steroids needs to be pursued.

Exposure to post-natal indomethacin for treatment of a PDA may also have long-term implications. Up to 25% of neonates

Key Points

- 1 Nutritional status in utero and the early post-natal period has implications for long-term cardiovascular health.
- 2 Premature infants are exposed to a number of insults post-natally that may affect glomerulogenesis and long-term renal health.
- 3 Ex-premature neonates should have their blood pressure checked routinely throughout childhood and into adulthood.

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exposed to indomethacin suffer acute renal failure.¹⁰ In a neonatal rat model, exposure to indomethacin and ibuprofen showed significant glomerular injury on electron microscopic examination but at 14 days did not reduce glomerular number.^{11,12} A recent study has shown increased numbers of podocytes in the urine of preterm neonates receiving indomethacin, suggesting that the drug induces glomerular injury at this critical time of ongoing glomerulogenesis.¹³ At present, intravenous indomethacin or ibuprofen are the drugs of choice to close a PDA. However, new studies into paracetamol as an alternative may present neonatologists with a safer option abrogating renal risk.¹⁴

The entity of preterm birth itself may result in reduced nephron numbers increasing risks of later renal and hypertensive disease. Gubhaju *et al.* have shown altered glomerular structure in 0.2–18% of glomeruli in the outer renal cortex of preterm baboons, which may have long-term implications on renal health.¹⁵ A recent premature mice study has shown a reduction in nephron number solely related to prematurity, which was associated with reduced glomerular filtration rate (GFR), proteinuria and adult hypertension.¹⁶ In a post-mortem study of human neonatal kidneys, those born premature and surviving for a period of time were shown to have accelerated maturation and abnormal glomerular morphology in comparison with stillbirth controls at the same gestation.¹⁷ Although there was no evidence of decreased renal volume in preterm infants at term-corrected age,¹⁸ a separate study has shown that at 20 years of age, the left kidney length and volume was smaller in preterm infants than term controls, particularly in females.¹⁹ As an extension of these histological and morphological findings, elevated BP has been found in a number of studies of extremely preterm babies at a variety of ages.^{20–22}

Clinical Scenario 2

Another common clinical scenario is the neonate that is delivered at 32 weeks gestation weighing 1000 g (<third centile) after an antenatal ultrasound showing reverse diastolic flow. The baby is commenced on feeds, and after a period of feed intolerance, progresses to full feeds and is eventually discharged home weighing 2500 g at 44 weeks gestation (<third centile). What factors place this baby at long-term cardiovascular/renal risk?

In utero growth restriction (IUGR) is now implicated in many health conditions later in life including obesity, insulin resistance, hypertension and diabetes.²³ There are a number of animal studies using uterine artery ligation as a model for IUGR looking at metabolic and renal consequences.^{24–26} Protein restriction is another method used in animal studies to produce IUGR in the offspring to look at cardiovascular and renal consequences.^{27–29} Nephron number has been associated with progression of renal disease and hypertension in human adults in two studies,^{30,31} and there are now a number of studies indicating that low birthweight contributes to end-stage renal disease.^{32–35} There is, unfortunately, no non-invasive way of determining nephron number in the living human. Since the first papers by Barker, Hales *et al.* and Osmond *et al.*,^{36–38} the number of studies associating low birthweight with cardiovas-

cular disease and diabetes have increased with a number of reviews and systematic analyses confirming the relationship.^{39–42}

Clinical Scenario 3

Unfortunately, this scenario is becoming increasingly frequent. A term baby is delivered weighing 2.1 kg at 36 weeks gestation to a woman with a body mass index (BMI) of 45, gestational diabetes and pre-eclampsia. The placenta showed evidence of chorangiosis and accelerated maturation with increased syncytial knot formation. Again, there are a number of potential risks for this baby for long-term metabolic and cardiovascular compromise.

This clinical example had two potential sets of adverse fetal outcomes: those associated with the growth-restricted baby described or those associated with the macrosomic neonate. With obesity becoming a major health problem in pregnant women, the added complication of gestational diabetes is a frequent finding. A recent large Swedish study has found that gestational diabetes resulted in a higher BMI in an 18-year-old male offspring, independent of maternal BMI.⁴³ This has also been found in a study from Jerusalem where offspring at 17 years of age were found to have a higher BMI and BP.⁴⁴ However, these findings have not been replicated in other studies,^{45,46} and a recent systematic review has not found a consistent finding of gestational diabetes with obesity in offspring.⁴⁷

Maternal obesity is related to poorer outcomes for both the mother and the fetus and is becoming a significant concern for later cardiovascular and metabolic outcomes.⁴⁸ Zhang *et al.* reviewed the animal evidence for maternal over-nutrition and peri-conceptional weight changes and resulting metabolic outcomes.⁴⁹ Maternal diabetes and pre-eclampsia appear to have an effect on BP in the first year of life, and this is particularly evident in those where placental dysfunction was noted on histology.⁵⁰ Birthweight has been shown to increase with both increasing maternal BMI and weight gain during pregnancy,⁵¹ and recently, two studies have shown that maternal obesity in pregnancy increases the risk of obesity in children 2 to 4 years of age.^{52,53} A recent cross-generational study has shown an association of maternal BMI enduring over three generations.⁵⁴ The human evidence now available is supporting the findings of animal models where maternal obesity has long-lasting implications on metabolic and cardiovascular outcomes of the offspring that may last for generations.

With these three case scenarios, there is then the issue of 'catch-up growth'. What is catch-up growth? Who does this apply to and should we be aiming for it? In the appropriately grown (10th–90th centile) premature neonate who has poor nutritional intake post-natally and falls below his or her original birth centile, the definition of catch-up growth has some conceptual framework for where that child's growth should be. However, for small for gestational age (SGA) infants, the centile at which they should have been born on is unknown unless regular in utero growth scans prior to the timing of onset of the growth restriction exist, indicating their original growth potential. It is likely that long-term renal dysfunction and hypertension is a consequence of multiple hits to the developing kidney, and one of these insults includes this notion of 'catch-up growth'. Catch-up growth in preterm infants, including

head circumference, is related to improved neurological outcomes.^{55–58} True catch-up growth in the appropriate for gestational age premature neonate with post-natal growth restriction may be appropriate terminology and an important goal in the early neonatal period. These neonates should be considered differently to the SGA neonate as the long-term cardiovascular and metabolic consequences are concerning in those born SGA who have 'catch-up growth'.^{59–71} For the SGA infant, perhaps a more accurate description is weight gain above birth centile. It is not entirely clear from these studies at which point weight gain above birth centile in the SGA child is most deleterious, but continued rapid weight gain after 2 years of age may be problematic, while continued poor growth in the first year of life also appears to be harmful.

Clinical Scenario 4

While attending a conference in Santiago, Chile, you visit a hospital clinic where you see a 6-year-old child with asthma. She was born to a mother from a poor rural centre, who prior to pregnancy had a BMI of 19. Her daughter had a birthweight of 2.7 kg at 39 weeks gestation (fifth centile). Since moving to Santiago, their diet has changed and she now weighs 26 kg (>90th centile). What potential long-term risks are there for this child?

This scenario is becoming more common in developing countries and has the potential to stretch already restricted medical resources. Stein *et al.* reviewed cohort studies from developing countries, which have looked at metabolic outcomes into adulthood.^{72–76} Continued growth failure in early childhood with increased weight gain in later childhood is associated with risk factors for cardiovascular disease including hypertension, glucose intolerance and body adiposity. Adaptations that have occurred to ensure survival during restricted nutrient supply become maladaptive when over nutrition occurs.^{77,78} The World Health Organization/Food and Agriculture Organization (WHO/FAO) report on 'Diet, Nutrition and the Prevention of Chronic Diseases' in 2003 predicted that obesity-related type 2 diabetes would become a global epidemic.⁷⁹ As a consequence, developing countries with stretched medical resources will now have to contend with the burden of chronic life-style diseases as well as infectious diseases.

Closing Comments

These four examples are situations that neonatologists and paediatricians face on a daily basis. As neonatal intensive care has improved, increasing numbers of extremely premature infants are surviving with reduced morbidity, and consideration must be given not only to their neurological outcome but long-term health consequences as well. It is difficult to extrapolate from the evidence available interventions during the neonatal period for the extremely premature neonate to minimise long-term health risks. However, with the available evidence trying to minimise known risk factors, as much as possible would be a logical approach. Attempting to reduce those risks would include minimising exposure to nephrotoxic drugs during glomerulogenesis, such as indomethacin and ibuprofen, and maximising nutrition to ensure that premature neonates grow along

their percentiles so that catch-up growth is not required. The SGA neonate should be considered differently from the extremely premature neonate, and weight gain above their birth centile during the first 2 years of life may be appropriate while avoiding rapid growth after the first 2 years of life. Parental awareness of the potential long-term health consequences of extreme prematurity and growth restriction is required, with focus placed on a healthy life-style continuing once the neonate is discharged home. Primary prevention continues to be of importance but frequently the most difficult to provide due to time restrictions and a lack of focus on child cardiovascular health. The incidence of hypertension in children is increasing and ranges from 1% to 10%,⁸⁰ but BP measurement in children is infrequently performed, and if done, elevated levels often go unrecognised.⁸¹ Discussing cardiovascular risk and obesity needs to start early in these particularly vulnerable groups of children to minimise long-term health sequelae.

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