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Hypoglycemia in the Newborn and Neurodevelopmental Outcomes in Childhood

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Severe and persistent neonatal hypoglycaemia is well known to be associated with neuroadversity but the effects of asymptomatic mild neonatal hypoglycaemia, common in the early post natal period, is unclear.[1] Approximately 30% of newborns have recognised hypoglycaemia risk factors which include maternal diabetes, prematurity, small for gestational age and macrosomia.[1] Difficulties in clinical recognition of neonatal hypoglycaemia have led to the practice of screening at risk infants and intervening with exogenous glucose when a low glucose threshold is breached. Lack of consensus on the glucose threshold for intervention and known inaccuracies in point of care measurements of glucose add to the challenges of evidence-based practise [2]. Interventions may also negatively impact breast feeding rates and bonding because of parental anxiety and separation and potential iatrogenic glucose reperfusion injuries with large glucose level fluxes are an additional concern.[3] Distinguishing between mild short-lived "transitional" neonatal hypoglycaemia and hypoglycaemia which requires intervention to avoid long term neurological compromise and developing optimal management strategies presents a major challenge to clinicians caring for at risk infants.

In the March 2022 edition of JAMA, follow up data from two additional prospective cohort studies in this area was published. The CHYLD (Children with Hypoglycemia and Their Later Development) study, a prospective New Zealand cohort study, recruited 614 eligible infants with at least one risk factor for hypoglycemia between 2006 – 2010.[4,5] Infants with known or suspected congenital hyperinsulinism or metabolic disorder were excluded. Recruited infants were screened with whole blood glucose measured on a blood gas analyser at intervals from 1-2 hour after birth until there was no further clinical concern (up to Day 7) , with parallel masked continuous glucose monitoring with offline calibration. Hypoglycemia was defined as a glucose level below 47mg/dl (2.6 mmol/L) and was managed with buccal, oral or IV glucose to maintain blood glucose above 2.6 mmol/L. A subgroup (n=237) who became hypoglycaemic were randomised to dextrose gel or placebo gel for management of initial hypoglycaemia. While McKinley et al previously reported

that those exposed to hypoglycemia exhibited significantly lower scores in executive function and visual motor function at age 4.5 years,[5] with the greatest impairment seen in those exposed to severe, recurrent and undetected hypoglycaemia compared to those not exposed, Shah et al report that by age 9-10 years, no difference in low educational achievement rates is seen between the groups.[4] This might suggest that neuroplasticity allows catch up in mid childhood. This reassuring outcome however contrasts with findings of an earlier prospective cohort study following 1395 children where brief transitional neonatal hypoglycemia was associated with academic underachievement at age 10 years [6]. Caution in over interpreting these reassuring findings is warranted given the very high levels of low educational achievement (48%) seen in the enrolled cohort of infants in the CHYLD study in both the hypoglycaemia exposed and non-exposed groups.

Edwards et al in the same edition reported the findings of a later prospective study (Hypoglycaemia Prevention with Oral Dextrose (hPOD trial)) which examined the effect of prophylactic dextrose gel on neurodevelopmental outcomes in infants at risk of hypoglycaemia.[7] Between 2015 and 2019, 2249 infants were enrolled into this double blinded randomised multi-centre trial from 18 centres in New Zealand and Australia. At risk infants were randomised to receive prophylactic dextrose 40% or placebo into the buccal mucosa at 1 hour of life, followed by breast feeding. Blood glucose levels were checked at 2 hours, with repeat checks as per local hospital protocols. Oral dextrose gel has been shown to reduce hypoglycaemia rates with no immediate adverse effects and no reduction in breast feeding rates at time of discharge or at age 6 weeks.[8,9,10] Edwards et al reported the 2 year follow up data of the 1197 New Zealand participants in the hPOD Randomized trial.[7] Neurosensory impairment was defined as blindness, hearing impairment requiring hearing aids, cerebral palsy, developmental delay based on Bayley

III score <85 or performance based executive function <1.5 below cohort mean. No significant difference was seen in neurosensory impairment between the groups randomised to dextrose gel vs. placebo (20.8% vs 18.7%, unadjusted risk difference [RD] 2.09% [95% CI, -2.42% - 6.60%] adjusted risk ratio [aRR] 1.13 [95%CI, 0.9 – 1.41]. Interestingly, the cohort assigned to dextrose gel had a significantly higher risk of motor delay (2.5% vs 0.7%; RD 1.81% [95% CI 0.40% - 3.23%] and significantly lower composite scores for cognitive (adjusted mean difference [aMD], -1.3 [95% CI -2.55 to -0.05], language(aMD, -2.16 [95% CI, -3.86 to -0.46]) and motor (aMD, -1.40 [95% CI, -2.6 to -0.2]) performance. Whilst dextrose gel at 200mg/kg has been shown to reduce the incidence of hypoglycaemia,[10] follow up data showed no benefit in reducing neurosensory impairment at 2 years of age, with prophylactic usage concerning for adverse outcomes in cognitive, language and motor performance. Further analysis of developmental outcomes in this cohort at school age will be important to assess if this finding persists, but caution in using dextrose gel prophylactically is currently warranted.

Together these studies suggest that the risk factors for hypoglycaemia (including prematurity, growth restriction and maternal diabetes) and their socioeconomic determinants may exert a significant overall effect on developmental outcomes. Given the overall increase in maternal diabetes incidence, neonatal hypoglycaemia rates are likely to rise. Targeted efforts to reduce

gestational diabetes are warranted given the developmental deficits seen in this vulnerable cohort. As technology and point of care glucose measurement accuracy improves, consistent practise in defining blood glucose thresholds for intervention and the glycaemic effect of interventions should be possible, facilitating more accurate evaluation of hypoglycaemia prevention and management strategies.

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