How Un Sweet! It is:

BAKING & CANDY MAKING SUPPLY

The Conundrum of What to Do for Transient Neonatal Hypoglycemia

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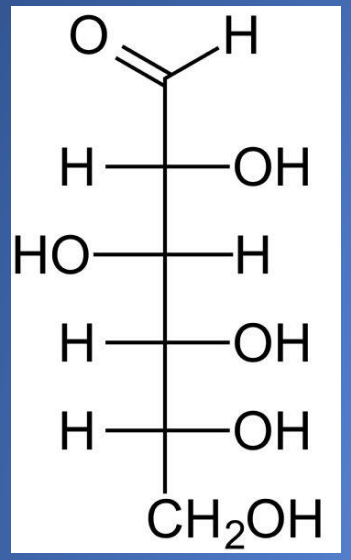
Departments of Pediatrics and OB/GYN

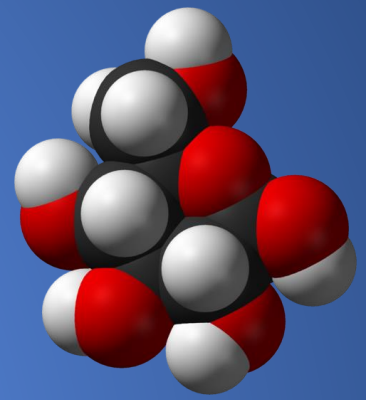
Florida Neonatal Neurologic Network Annual State Meeting

August 4, 2018

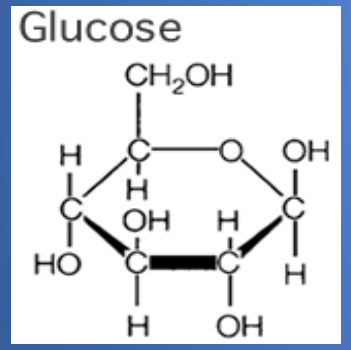
PennState Health
Children's Hospital

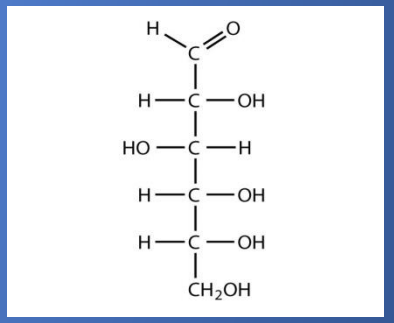


Disclosure Statement



- I have no relevant financial relationships with the manufacturers of any commercial product and or providers of commercial services discussed in this activity





Except that I live in…

The Sweetest Place on Earth

Objectives

1. Normal newborn glucose homeostasis
2. Neonatal transient hypoglycemia-why are newborns more susceptible?
3. Contentious issues
4. AAP vs Pediatric Endocrine Society (PES) guidelines
5. Association between transient newborn hypoglycemia and long-term educational outcomes
6. Do early feedings affect glucose homeostasis?
7. CHYLD-Sugar Babies Study
8. Prophylactic treatment studies
9. Hypoglycemia and neurodevelopmental outcomes
10. Influence of glycemic status and hypocapnia on outcomes in HIE

A Story…

- At the University of Arkansas, universal newborn glucose screening has been in effect since the 1970s

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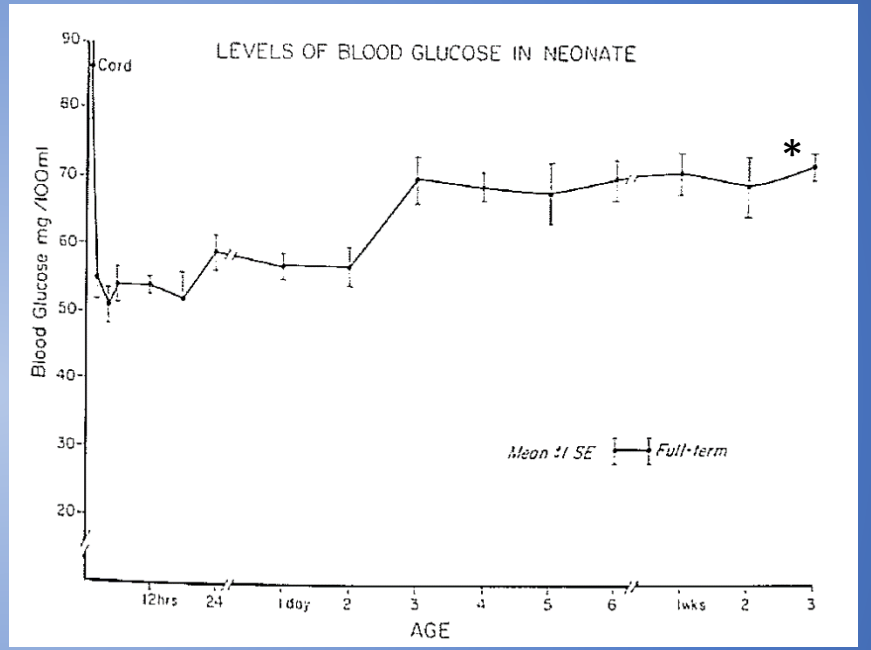
- 100,000 newborns
- **Let's study it**

Normal Newborn Glucose Homeostasis

- Glucose is the major energy substrate for placental and fetal metabolism
- At term, fetal levels ~10 mg/dL < mother
- Maternal glucose concentrations 70-90 mg/dL
- In normal term newborns, levels reach a nadir to 55-60 mg/dL between 1-2 hours
- Over the first few days, levels steadily increase to >70 mg/dL



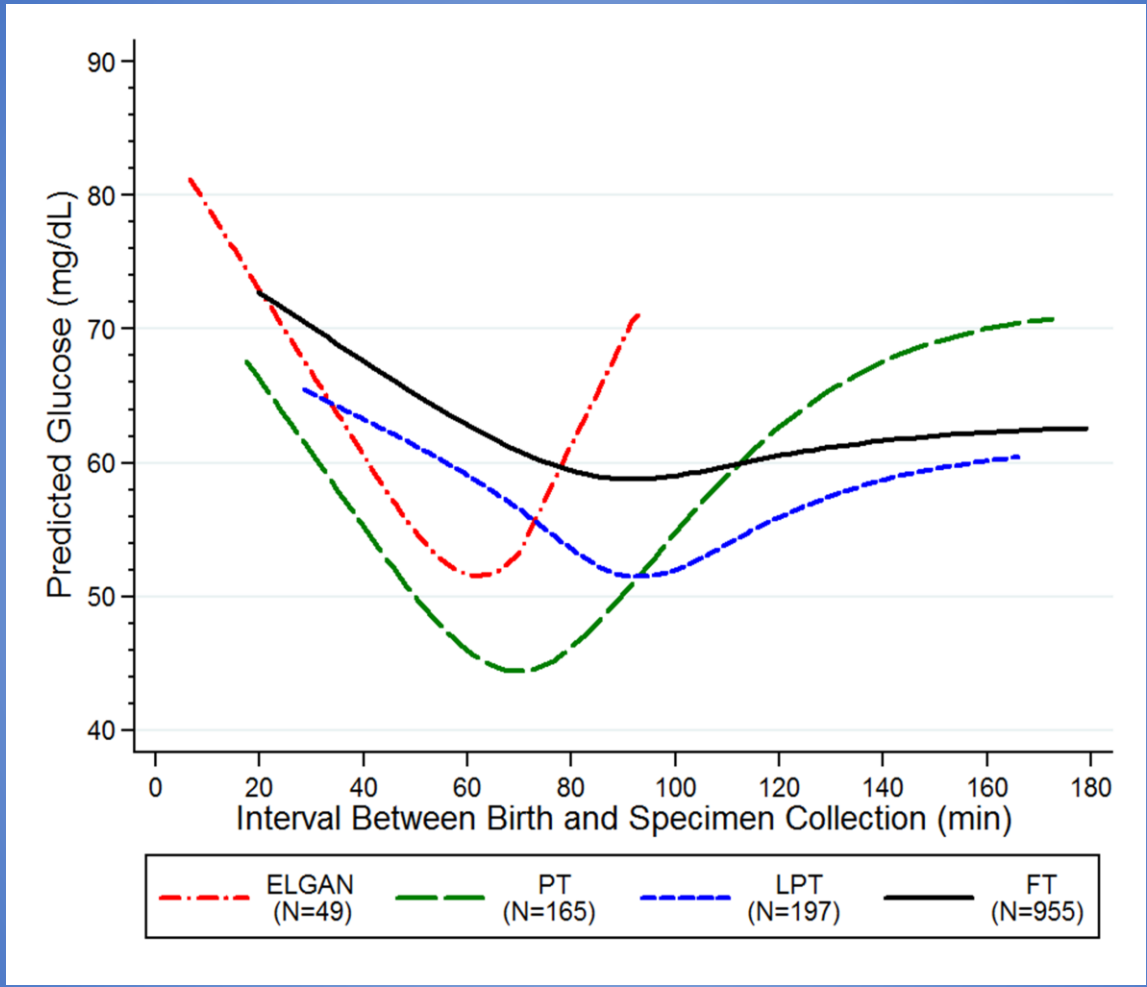
Cornblath, *NEJM* 1965;273:378-81

PennState Health Children's Hospital

J Pediatr 2015; 166:1520-5

*multiply by 1.15 to convert to plasma levels

Glucose Nadirs



At birth, the continuous utero-placental umbilical infusion of glucose ends and levels nadir during the first several hours

Kaiser, et al. *Neonatology*, 2018;113(4):353-9

Breastfeeding in the Normal Newborn

- During the DOL #1, breastfed newborns consume very few calories
  - Average volume of colostrum ingested per feeding is only 0.5-1.6 ml/kg on DOL #1
  - First-day colostrum has 20% of the lactose concentration of mature breast milk
  - Ketones are not elevated in breastfed infants on DOL #2

Br J Nutr 1984;52:87-95, *Am J Clin Nutr* 1988;48:1375-86, *J Am Coll Nutr* 2001;20:209-11, *Am J Clin Nutr* 1991;54:81-92, *Am J Dis Child* 1986;140:933-6

Hypoglycemia—an Imbalance between Glucose Supply and Utilization

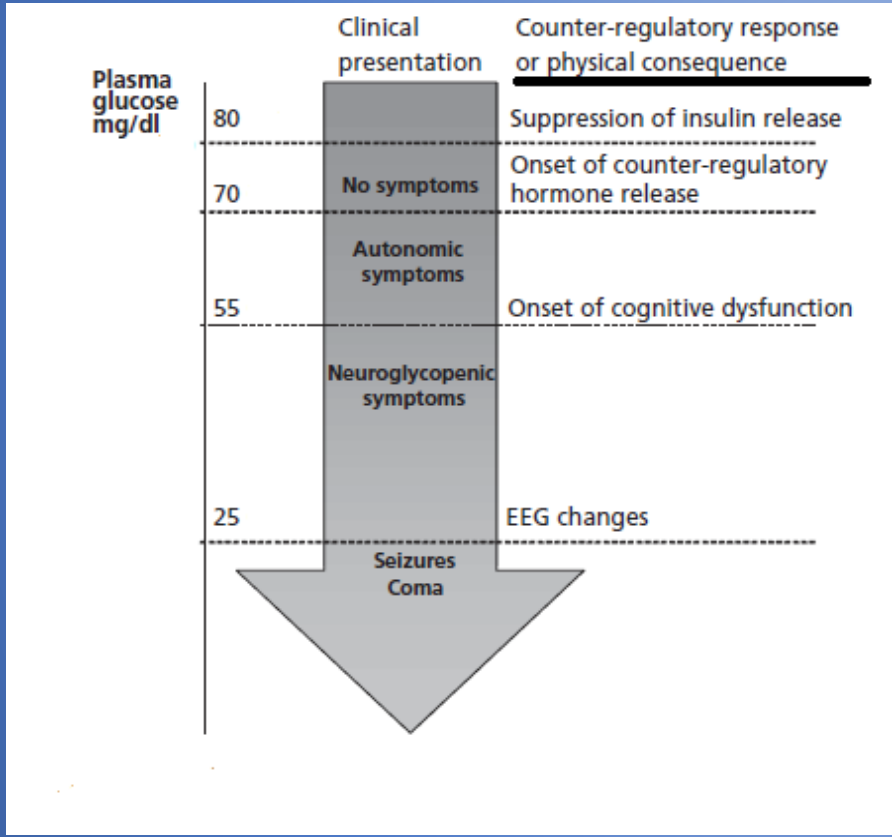
- Decreased substrate (e.g., IUGR)
- Hyperinsulinism
- Endocrine abnormalities
- IEM

Glucose Supply

Glucose Utilization

Responses of Adults and Newborns to Specific Glucose Concentrations

Adults



Diabetic Emergencies, 2012

Responses of Adults and Newborns to Specific Glucose Concentrations

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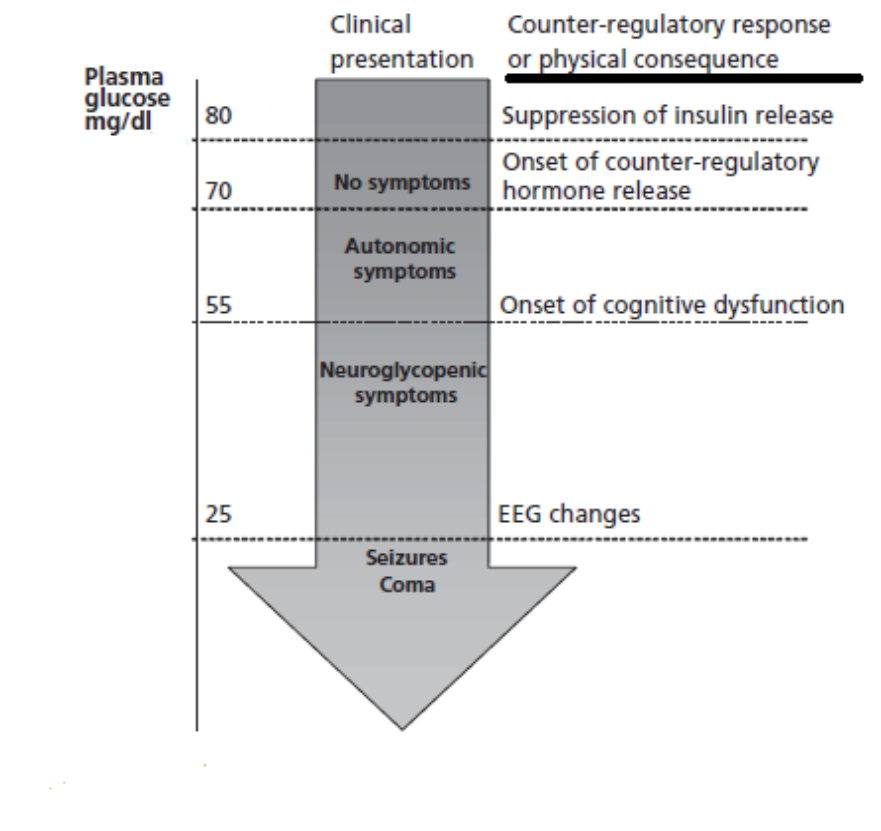
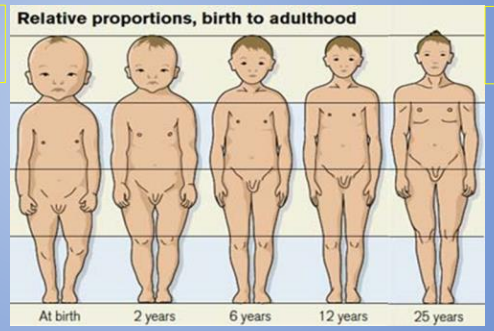


Newborns

Why are Newborns More Susceptible to Hypoglycemia?

- The newborn brain uses glucose almost exclusively as an energy substrate, and can account for up to 90% of the total glucose consumption
- Cerebral glycogen stores are low
- High brain-to-body weight of newborns result in a proportionately higher glucose demand than adults

13.4%



2.3%

- While alternative fuels such as ketone bodies and lactate can be used by the brain, the immature counterregulatory response limits availability of these molecules, especially early on
- Thus, newborns are especially vulnerable to problems impairing normal glucose homeostasis during transition from fetal to neonatal life

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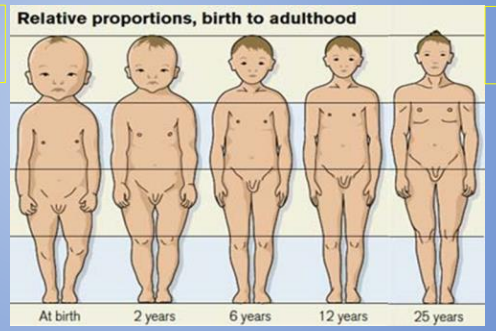

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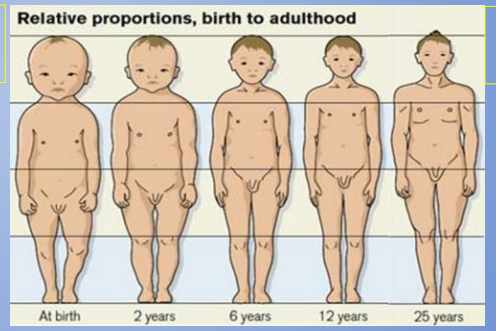

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Hypoglycemia

- Transient neonatal hypoglycemia is common affecting up to 15% of healthy infants and up to 50% of at-risk newborns
- Its incidence may be increasing because of increases in maternal obesity and gestational diabetes
- Transient neonatal hypoglycemia (first 48–72 hours of life)
  - Hypoketotic
  - Due to immature counterregulatory pathways resembling congenital hyperinsulinemia
  - It is associated with a lowered glucose threshold for suppression of insulin secretion
  - Inappropriate preservation of liver glucose stores

J Pediatr 2015; 166:1520-5

Hypoglycemia: Evidence- vs Eminence-based

- …no substantial **evidence-based** progress in defining what constitutes newborn hypoglycemia and its relation to brain injury
- Monitoring, prevention, and treatment of newborn hypoglycemia remains largely empirical, and has been debated for more than 50 years
- Guidelines make practical recommendations for screening and managing neonatal hypoglycemia based on expert consensus **(…"eminence-based"…)** rather than evidenced-based long-term follow-up studies
- Some international bodies recommend lower (AAP) and higher (PES) thresholds for treatment and management, which shows the paucity of high-quality evidence. ***There is no high-quality evidence to guide the management of transient neonatal hypoglycemia!***
- Neonatal hypoglycemia may be one of the most preventable causes of brain injury, on the other hand, overtreatment may lead to decreased breastfeeding and brain changes from repeated pain from heel lances, and treatment has never been shown to be beneficial

Pediatrics 2011; 127:575-9 (AAP); *J Pediatr* 2015; 166:1520-5 (PES)

Clinically Significant Hypoglycemia

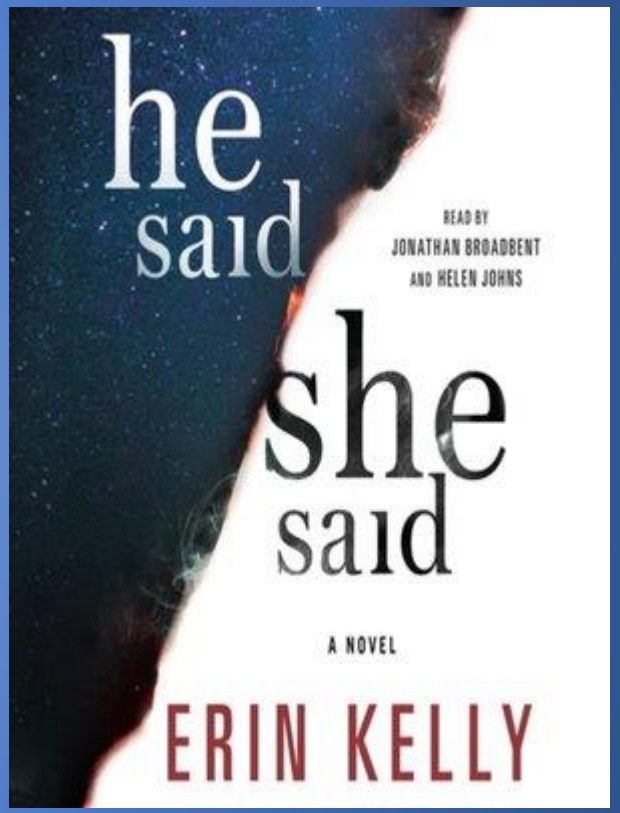
- "the definition of clinically significant newborn hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology…"

--Marvin Cornblath, 2000

Pediatrics 2000; 105:1141-5

She Said, He Said

vs



She Said, He Said

-  "the experimental and human clinical data are clear that hypoglycemia (<45 mg/dL) is injurious to the newborn brain and must be aggressively managed to avoid adverse consequences."

She Said, He Said

- “the experimental and human clinical data are clear that hypoglycemia (<45 mg/dL) is injurious to the newborn brain and must be aggressively managed to avoid adverse consequences.”
-  “we strongly disagree. This statement is supported neither by the clinical data in humans nor experimental data from animal studies.”

She Said, He Said

-  "that would be a misinterpretation of my commentary. There are, indeed, no data to support such a conclusion."

She Said, He Said

- "that would be a misinterpretation of my commentary. There are, indeed, no data to support such a conclusion."

-  such an unfounded statement has the potential to promote unnecessary invasive interventions, failed breastfeeding, anxiety among parents, and other potential complications from overdiagnosis and overtreatment."

She Said, He Said

- "the conclusion in my commentary was ambiguous, and such a misinterpretation could lead to overtreatment of healthy infants and medico-legal misinterpretation…"

She Said, He Said

- "the conclusion in my commentary was ambiguous, and such a misinterpretation could lead to overtreatment of healthy infants and medico-legal misinterpretation…"

-  If 'she' has new objective data to support her statement, we would all welcome the publication of this information. If not, we would be better served if she qualified her statement or, in the absence of any specific information, retracted it completely."

She Said

-  “In conclusion, I am grateful to ‘him’ for balancing this pendulum with the evaluation of the healthy well infant vs the at-risk newborn. The commentary was focused on the at-risk or “sick” newborn, and should not be extrapolated to healthy newborns, for whom very prolonged and severe hypoglycemia would be required to lead to cerebral injury.”

Knowledge Gaps with Defining Neonatal Hypoglycemia

- Knowledge gaps exist about the definition of neonatal hypoglycemia, specific cutoffs or thresholds (mg/dL), management, and clinical significance ….even after >**6,000 articles**

J Pediatr 2009; 155:612-7

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25

AAP

?

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47

Sugar Babies

J Pediatr 2009; 155:612-7

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Flaws in the Definition of Hypoglycemia

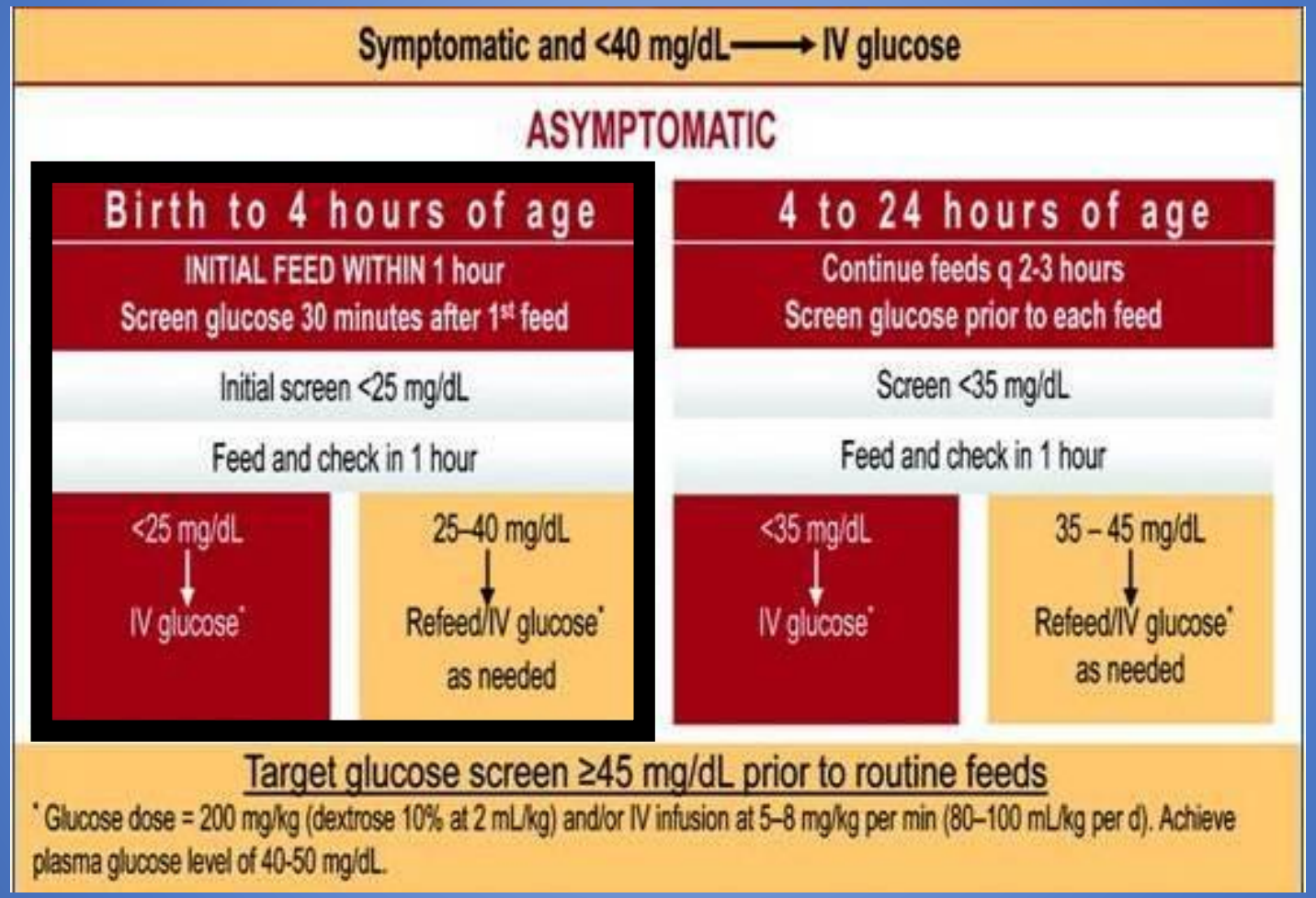
1. Clinical: ("symptoms"), similar non-specific manifestations occur with other neonatal problems
2. Epidemiological: cutoff values (<10%-ile, >2 SD) are not necessarily abnormal or cause injury
3. Physiologic: effects on CBF, EEG, and hormonal responses
4. Functional: (neurodevelopmental outcome), most studies lack non-hypoglycemic controls, do not control for SES and parental education, use different glucose cutoffs, have short follow-up, do not consider other pathologies, and have small numbers of asymptomatic infants

- This report provides a practical guide and algorithm for the screening and subsequent management of neonatal hypoglycemia, in late preterm, and term SGA, IDM/LGA infants
- …expert panel…
- …it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed

Pediatrics 2011; 127:575-9

Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

AAP



2011

Pediatrics 2011; 127:575-9

Pediatric Endocrine Society (PES)

- "Transitional Neonatal Hypoglycemia"
  - First 48 hours, focus on stabilizing glucose concentrations
    - "For high-risk neonates without a suspected congenital hypoglycemia disorder, we suggest the goal of treatment to maintain a [pre-prandial] plasma glucose concentration **>50 mg/dL** for those aged <48 hours"
  - After 48 hours, persistently hypoglycemic infants should be worked-up to determine etiology

2015

J Pediatr 2015; 166:1520-5, *J Pediatr* 2015; 167:238-45

Recurrent, Prolonged, and Severe Neonatal Hypoglycemia is Associated with Poor Long-term Neurodevelopment and Neurocognitive Function (and brain damage)

"substantial controversy, however, remains as to whether asymptomatic [transient] hypoglycemia actually causes brain damage"

- Cornblath et al

- Additionally, many pediatricians and researchers consider transient early asymptomatic hypoglycemia a normal physiologic phenomena that is not associated with harm

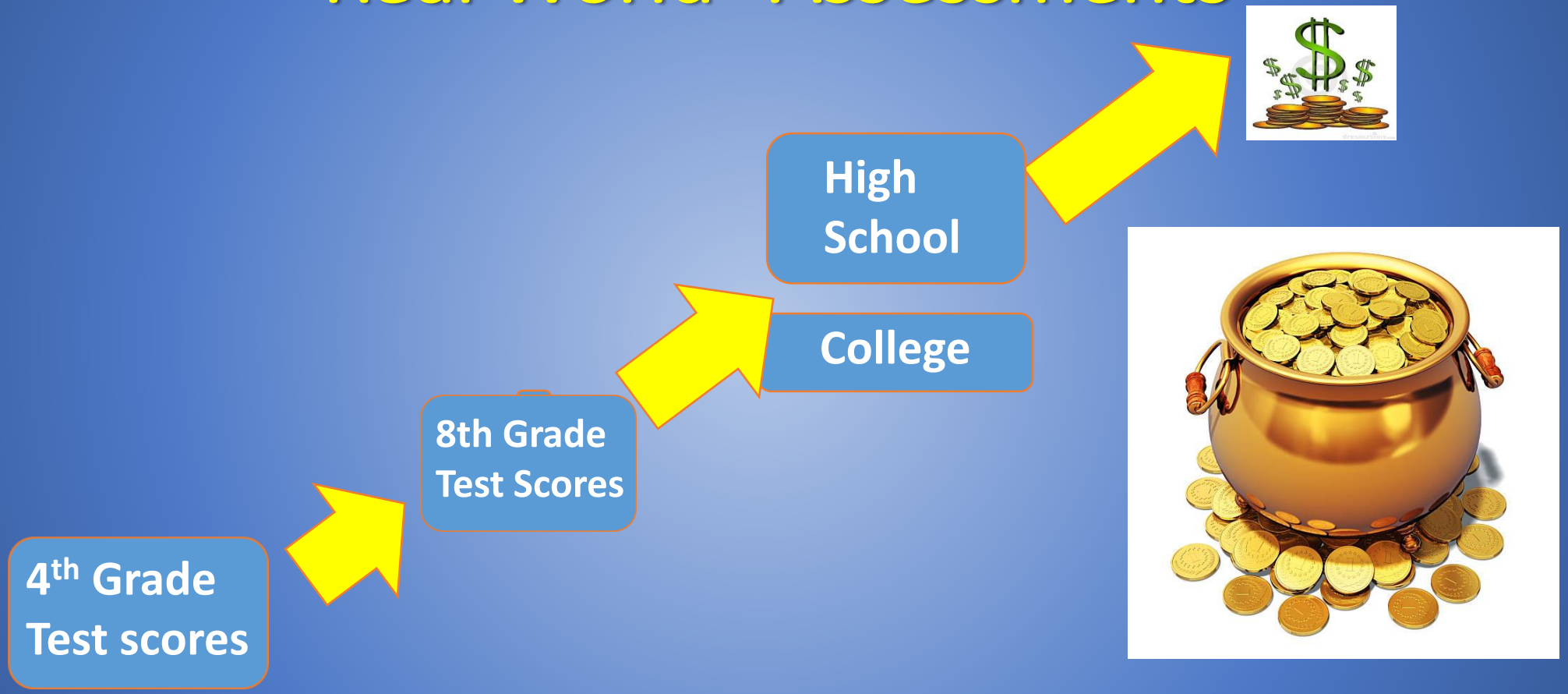
Pediatrics 2000; 105:1141-5

Objective

- Evaluate if early transient neonatal hypoglycemia is associated with school-age academic performance
  - A large sample size
  - Study sample of all newborns (not just an at-risk infants)
  - Universal newborn glucose screening, since 1970s
  - Adjust for multiple covariates including maternal education and SES
  - Unbiased outcome (4^{th} grade achievement tests)

JAMA Pediatr 2015; 169:913-21

4th Grade Achievement Tests: "Real World" Assessments



JAMA Pediatr 2015; 169:913-21

Hypothesis

- Transient neonatal hypoglycemia (a single low value followed by a second value above a cutoff) during the early newborn period is associated with poor long-term academic performance (achievement tests)
  - Glucose cutoffs:
    - <30, <35, <40, <45, and <50 mg/dL

JAMA Pediatr 2015; 169:913-21

Unique Data and Resources Available in Arkansas

- All newborns had glucose screening during 1st 3 hours (universal glucose screening)
- Plasma glucose with glucose oxidase method
  - NICU lab with turn around time of 25 min
- Glucose values available on >100,000 newborns (from 1970s)
- "No Child Left Behind"
  - Achievement tests in literacy and math 1st–8th grade
  - All Arkansas public school students
  - Arkansas Department of Education longitudinal database, since 1997
- Newborn data conservatively matched to student data: SSN, DOB, and names

JAMA Pediatr 2015; 169:913-21

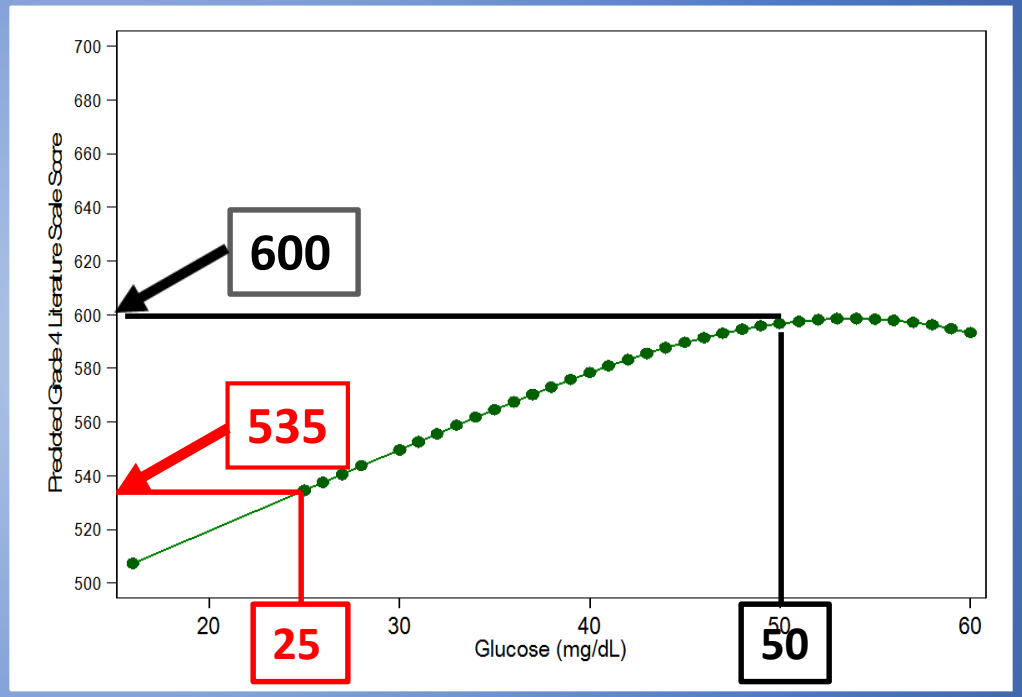
Arkansas Dataset

- Newborn data from 1998 (chart review)
  - All newborns 23-42 weeks' gestation (n=1,943)
  - Exclusions: major congenital anomalies, chromosomal abnormalities, and those with recurrent hypoglycemia
- 4th grade test scores from 2008
  - 10 years of age
  - Matched 1,395 (72%) newborn-test score data
- Matched and unmatched newborns essentially equivalent

JAMA Pediatr 2015; 169:913-21

Initial Glucose Concentrations in Healthy Term Newborns were Associated with 4th Grade Literacy Achievement Test Scores

- Definition of "healthy"
  - Full term (≥37 weeks)
  - AGA (10th–90th %-ile)
  - Apgar score[5] ≥7
  - No maternal DM or substance abuse
  - No polycythemia



Multivariate Logistic Regression

- Primary outcome: proficiency on 4th grade tests
  - Covariates used in the final models:
    - Transient hypoglycemia (using many cutoffs), gestational-age group, gender, race, insurance status (proxy for SES), maternal education level, gravidity, and multifetal gestation
  - Stepwise backward elimination method
  - **Other covariates considered for the models**: size for gestational age, 5-min Apgar, delivery route, meconium, polycythemia, chorioamnionitis, sepsis, maternal DM, substance abuse, prenatal care, PROM, smoking, and PIH

JAMA Pediatr 2015; 169:913-21

Multivariable Logistic Regression (<40 mg/dL cutoff)

TABLE 3. Final Models of Multiple Logistic Regression Predicting Achievement-test Proficiency

	Literacy		Mathematics	
Variable	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Hypoglycemic (<40 mg/dL)	0.43 (0.28-0.67)	<.001	0.51 (0.34-0.78)	.002

After adjusting for myriad factors, the odds of being proficient for normoglycemic newborns were about 2 times that of hypoglycemic newborns

JAMA Pediatr 2015; 169:913-21

<35, <40, and <45 mg/dL Cutoffs for Transient Hypoglycemia were Significant

Glucose Cutoff (mg/dL)	Literacy	Mathematics
<30	.385	.103
<35	.008	.006
<40	<.0001	.002
<45	.004	.137
<50	.102	.419

JAMA Pediatr 2015; 169:913-21

Weaknesses

- Retrospective data
- Timing of glucose-specimen collection at discretion of bedside nurses
- Treatment decisions based on neonatologist (and/or residents) *du jour*, no clear management policy
- Did not account for 10 years of personal characteristics, environmental influences, and diagnoses

JAMA Pediatr 2015; 169:913-21

Strengths

- Universal newborn glucose screening, study not biased by selection of special populations
- Plasma glucose concentration (glucose oxidase) determination routinely performed at a similar time after birth (rapid turn around time)
- Large study sample
- Follow-up 10 years with 72% of newborns
- Objective unbiased outcomes used
- Early transient newborn hypoglycemia was associated with lower achievement test scores at age 10 years

JAMA Pediatr 2015; 169:913-21

Important Considerations

- Given that the findings are serious and contrary to expert opinion, the results need to be validated in other populations before universal newborn glucose screening should be adopted
- Perhaps, we can mobilize newborn nurseries (in the future) to maintain iv catheters for glucose infusions
- or, perhaps, we should use 40% dextrose gel

JAMA Pediatr 2015; 169:913-21

Does Early Feeding Affect Initial Glucose Concentrations?

The Effect of Early Feeding on Initial Glucose Concentrations in Term Newborns

Yin Zhou, MD[1], Shasha Bai, PhD[2], Joshua A. Bornhorst, PhD[3], Nahed O. Elhassan, MD, MPH[4], and Jeffrey R. Kaiser, MD, MA[5]

(J Pediatr 2017;181:112-5)

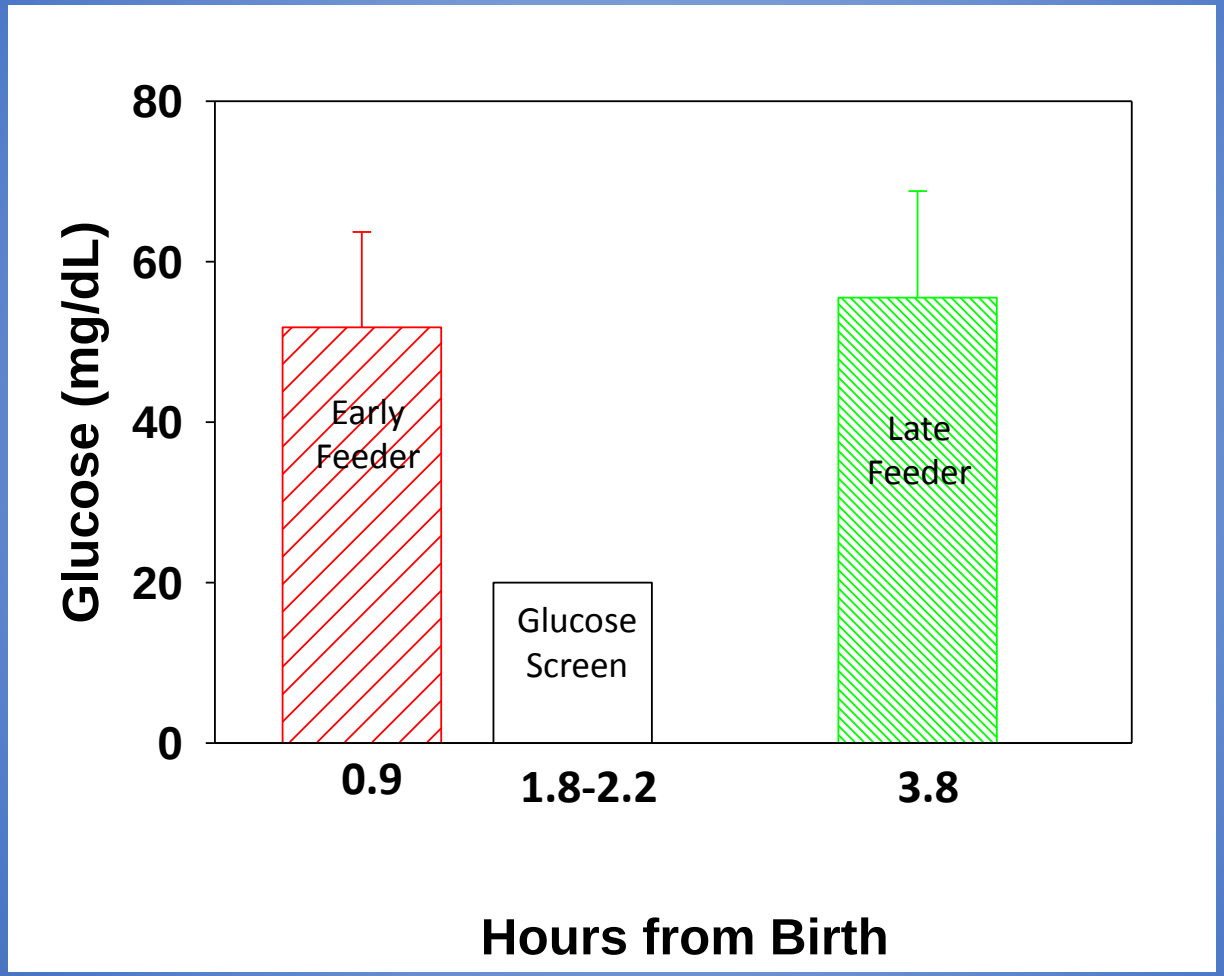
Objective To evaluate the influence of early feeding on initial glucose concentrations in healthy term newborns who were not at risk for hypoglycemia.

Study Design

- Retrospective observational trial
- Initial plasma glucose compared in healthy term infants (not at-risk of hypoglycemia) who were fed:
  - before (early feeders)
  - after (late feeders) their initial glucose screens
- Univariate and multivariate analyses

J Pediatr 2017;181:112-5

Glucose Concentrations for Early and Late Feeders in Relation to the Glucose Screen



J Pediatr 2017;181:112-5

Breastfed vs Formula-fed

Early vs Late Feeders

- In all infants, breast or formula-fed, initial glucose concentrations were about 3-4 mg/dL lower (and not higher) for early vs late feeders

J Pediatr 2017;181:112-5

Conclusion and Speculation

- Early feeding in otherwise healthy term newborns did not increase initial glucose concentrations compared with fasted (i.e., late feeding) infants, irrespective of breast or formula feeding
- Before direct evidence is available, our observations that early feeding does not increase glucose concentrations in non-at risk newborns, may be instructive for managing early asymptomatic hypoglycemia in at-risk newborns

J Pediatr 2017;181:112-5

CHYLD Study Group

Children with Hypoglycaemia and their Later Development

Jane Harding, Principal Investigator

Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial

Deborah L Harris, Philip J Weston, Matthew Signal, J Geoffrey Chase, Jane E Harding

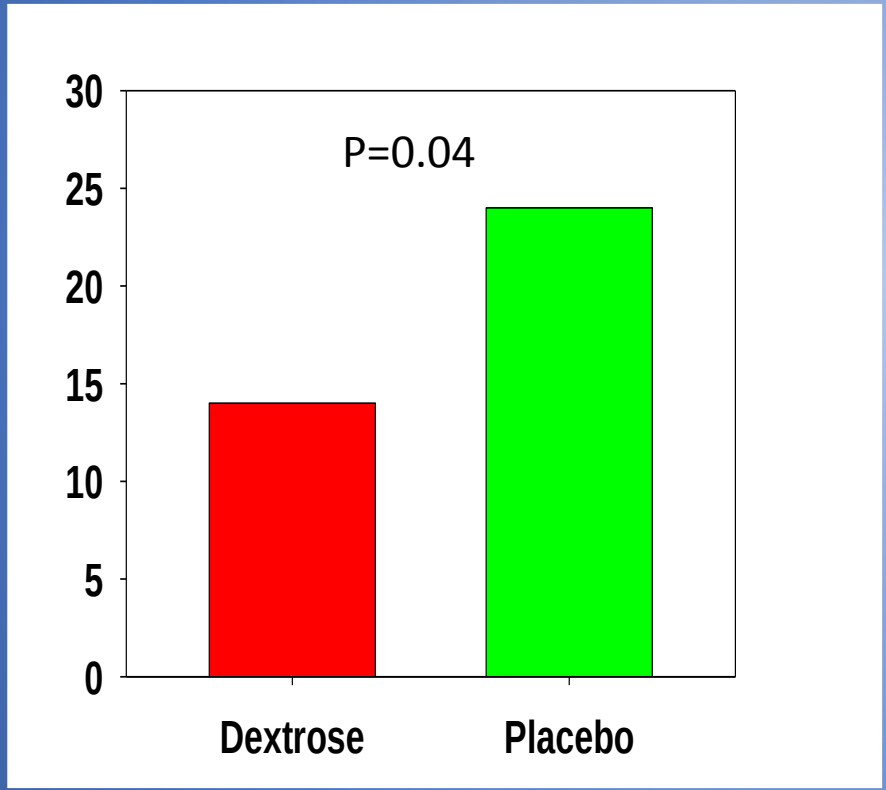
Lancet 2013; 382: 2077–83

- Is treatment with 40% dextrose gel (buccally applied) more effective than feeding along for reversal of neonatal hypoglycemia in at-risk babies?
- RCT
- 40% dextrose (n=118) vs placebo (n=119) gel
- 1°outcome: treatment failure—defined as BG concentration <47 mg/dL after 2 treatment attempts
- 2°outcome: NICU admission for the treatment of neonatal hypoglycemia

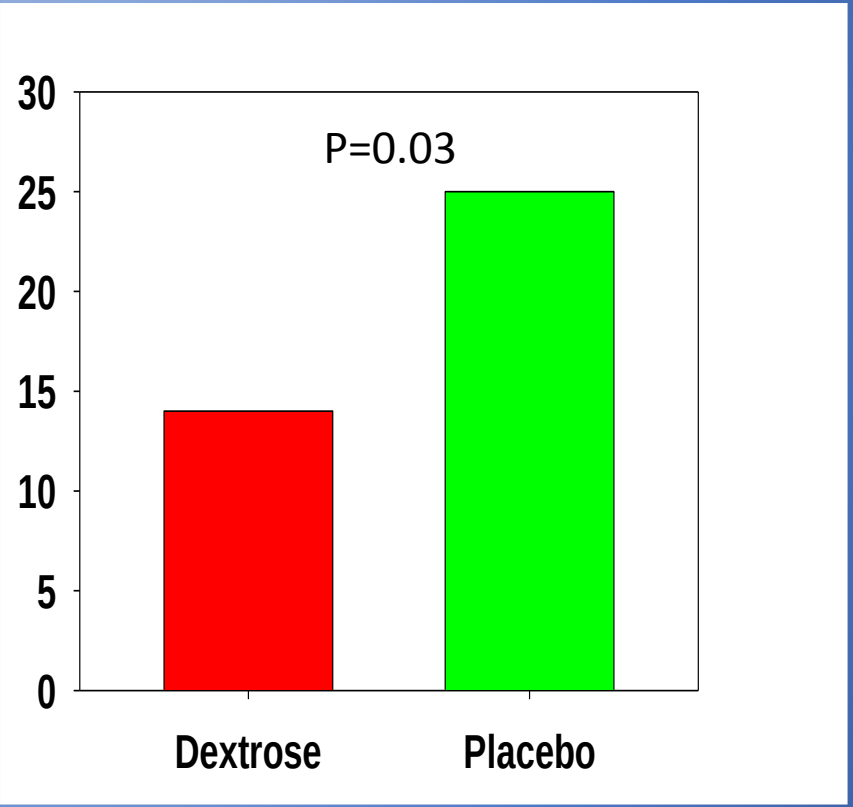
Lancet 2013;382:2077-83

Sugar Babies Study: Results

% Treatment Failure



% NICU Admission for Hypoglycemia



PennState Health Children's Hospital

Lancet 2013;382:2077-83

Does Prophylactic Dextrose Gel Prevent Neonatal Hypoglycemia?

A Pilot Study

Sarah M. Coors, BSN, DO, FAAP

Neonatal-Perinatal Medicine Fellow at Texas Children's Hospital

Pediatr Res 2018;198:156-61

Background

- 40% dextrose gel, applied to the buccal mucosa, has been shown in the Sugar Babies Study to safely treat ***established*** transient neonatal hypoglycemia
- We wondered if prophylactic dextrose gel provided to at-risk newborns would prevent or decrease transient neonatal hypoglycemia

Pediatr Res 2018;198:156-61

Hypotheses

Dextrose gel given prophylactically to at-risk newborns, compared to feeding alone, will:

1. Prevent/decrease transient neonatal hypoglycemia

and

2. Decrease NICU admissions for intravenous dextrose

Pediatr Res 2018;198:156-61

Design/Methods

- Quasi-experimental study design
- Study entry based on researcher availability:
  - After birth, cases (n=75) were given prophylactic dextrose gel after the first feeding
  - Others served as controls(n=188)
- Consent obtained prenatally
- Inclusion: Late preterm, IDM, <2500 g, or >4000 g
- Exclusion: symptomatic, after birth did not meet GA or BW criteria, chromosomal/congenital anomalies

Pediatr Res 2018;198:156-61

Prophylactic Dextrose Gel Procedure

Birth

Feeding

Dextrose Gel
0.5 ml/kg

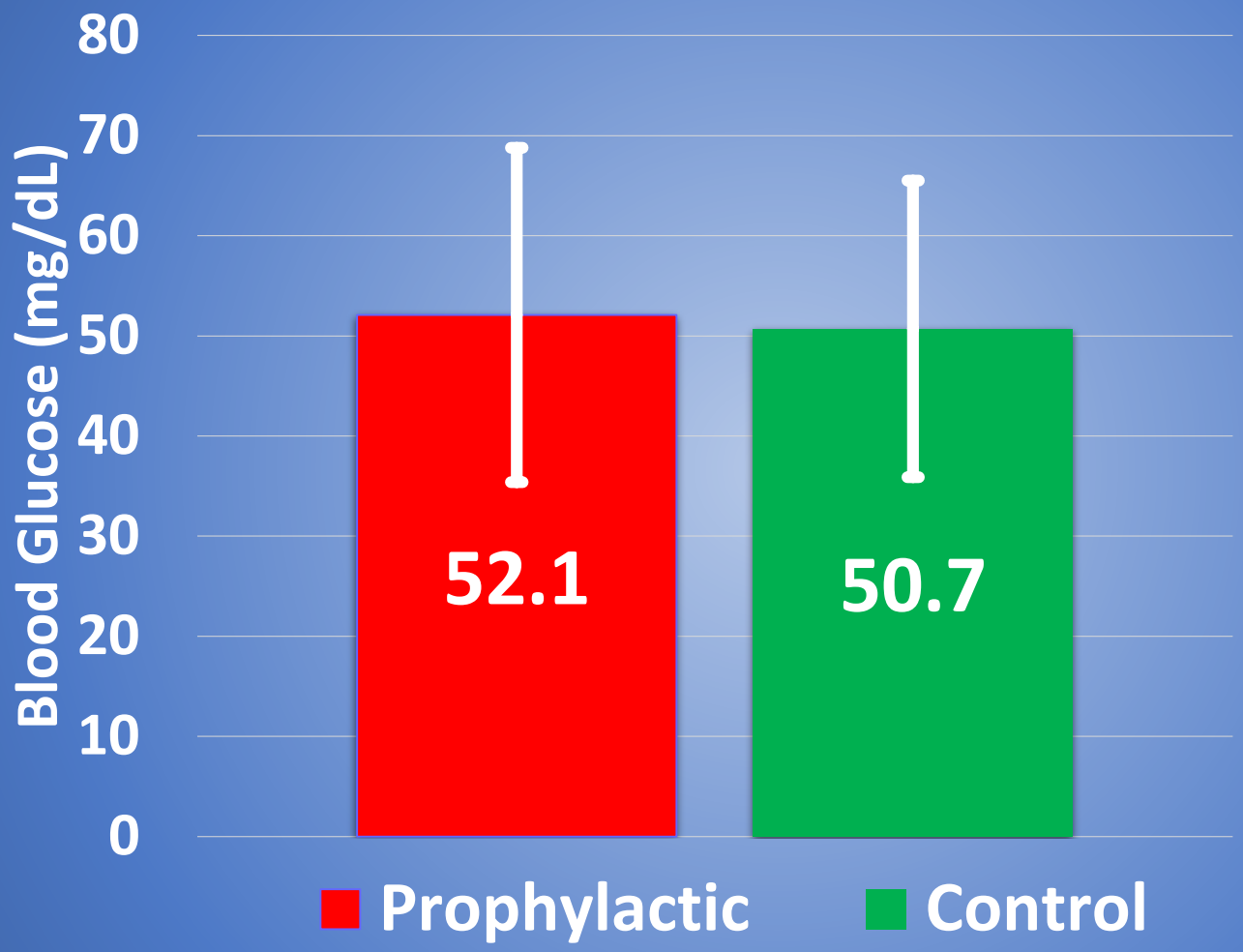
Control Group

BG checked 30
min later

PennState Health
Children's Hospital

Pediatr Res 2018;198:156-61

No Difference in 1st Blood Glucose



P=0.79
Univariate

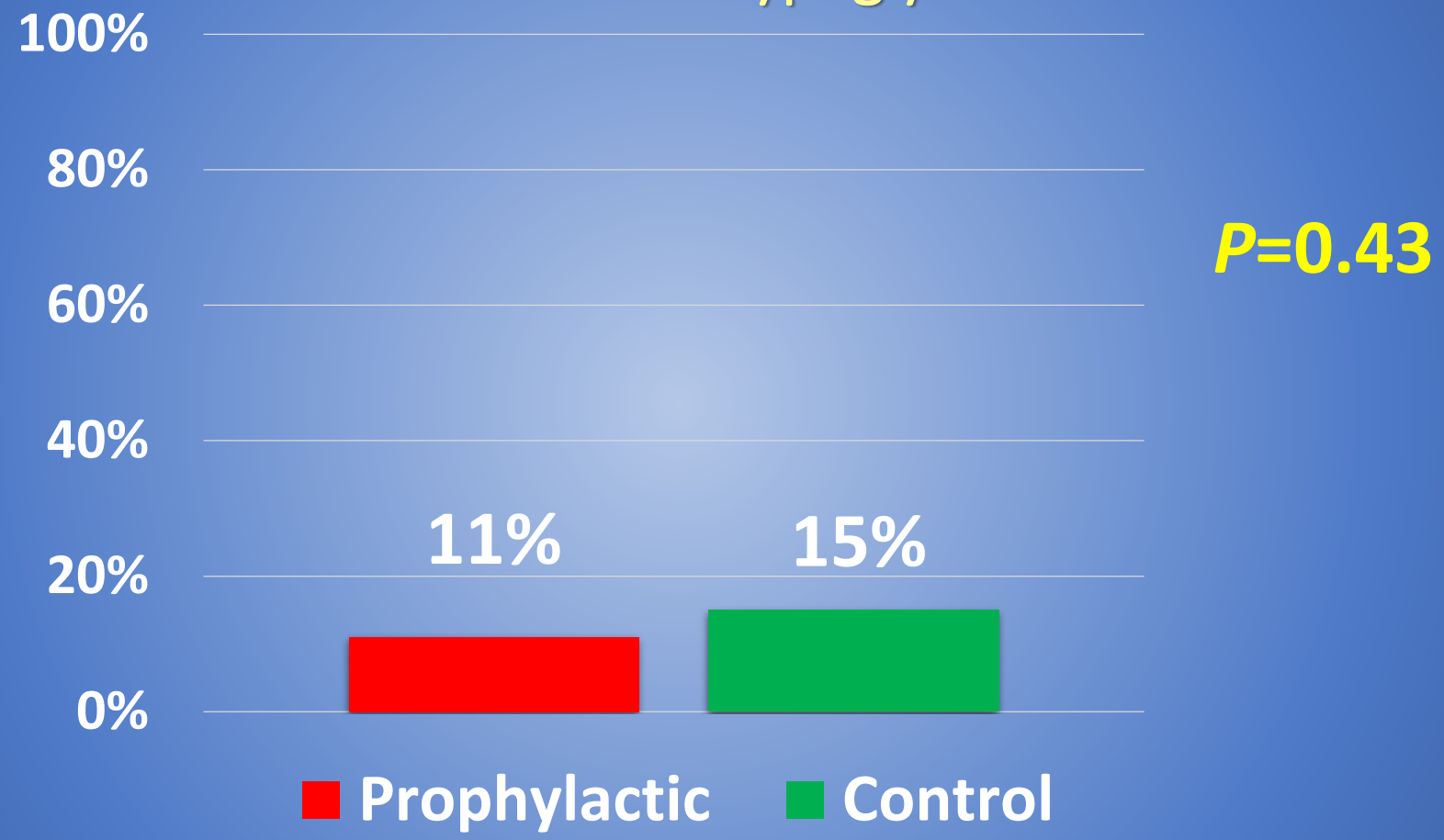
P=0.22
Multivariate

PennState Health
Children's Hospital

Pediatr Res 2018;198:156-61

No Difference in NICU Admission

for treatment of hypoglycemia



P=0.43

PennState Health Children's Hospital

Pediatr Res 2018;198:156-61

Conclusion/Speculation

- Prophylactic dextrose gel given to at-risk newborns immediately after the initial feeding did not increase blood glucose concentrations, or NICU admission for the treatment of neonatal hypoglycemia compared to feeding alone
- Exogenous glucose may not influence glucose homeostasis during the first hours after birth

Pediatr Res 2018;198:156-61

Conclusion/Speculation

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- Exogenous glucose may not influence glucose homeostasis during the first hours after birth

i.e.,

- Perhaps, **"you cannot fool Mother Nature"**

Pediatr Res 2018;198:156-61

After the Study was Completed, and During Data Analysis…

Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study)

CHYLD

Joanne Elizabeth Hegarty[1,2], Jane Elizabeth Harding[1], Gregory David Gamble[1], Caroline Anne Crowther[1], Richard Edlin[3], Jane Marie Alsweiler[1,2,4]*

PLOS Medicine | DOI:10.1371/journal.pmed.1002155 October 25, 2016

Pre-hPOD Study

- RCT
- New Zealand, CHYLD Study Group
- At-risk newborns were provided:
  - Dextrose gel 200 mg/kg (single dose) or 400 mg/kg (double dose)
    - Either once at 1 hour (after breastfeeding)
    - Or, 3 additional doses, pre-prandial, during the first 12 hours
  - Placebo gel: 1 or 4 doses

PLOS Med 2016; 10.1371/journal.pmed.1002155

Pre-hPOD Study

- 1º outcome: hypoglycemia (<47 mg/dL) during 48 hours
- 2º outcome: admission to the NICU for hypoglycemia

Results

- Newborns randomized to a single prophylactic dose of 200 mg/kg had the lowest risk of hypoglycemia (*P*=0.04)
- Newborns who received any prophylactic doses of dextrose gel were less likely to be hypoglycemic (*P*=0.03)
- NICU admissions for hypoglycemia were less common (RR 0.46, CI 0.21-1.01, P=0.05)

PLOS Med 2016; 10.1371/journal.pmed.1002155

Coors' Study vs CHYLD Study (Pre-hPOD)

Coors' Study

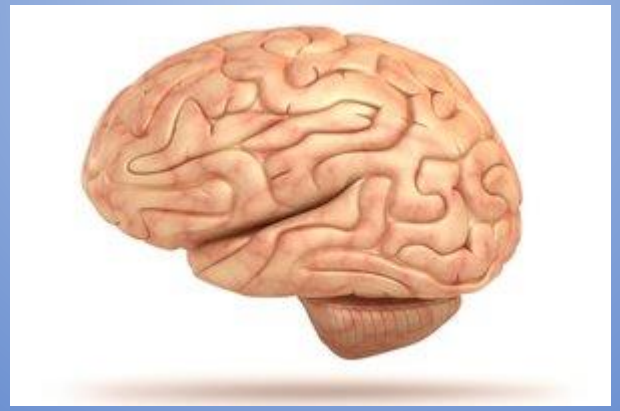
- Quazi-experimental
- Insta-Glucose®
- n=75 prophylactic, 188 controls
- Given at ~1hour
- Glucometer (glucose dehydrogenase)
- Evaluated 1st glucose concentration

Pre-hPOD

- RCT
- Compounded gel
- n=277 dextrose, 138 placebo
- Given at ~1hour
- Glucometer (glucose oxidase)
- Evaluated all glucose concentrations during 48 hours

Pediatr Res 2018;198:156-61, *PLOS Med* 2016; 10.1371/journal.pmed.1002155

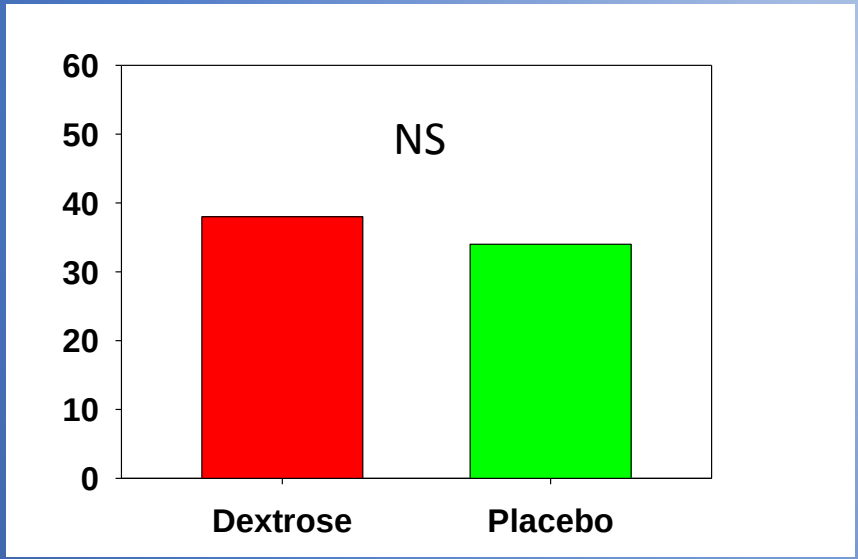
Neurodevelopment/Cognition after Hypoglycemia



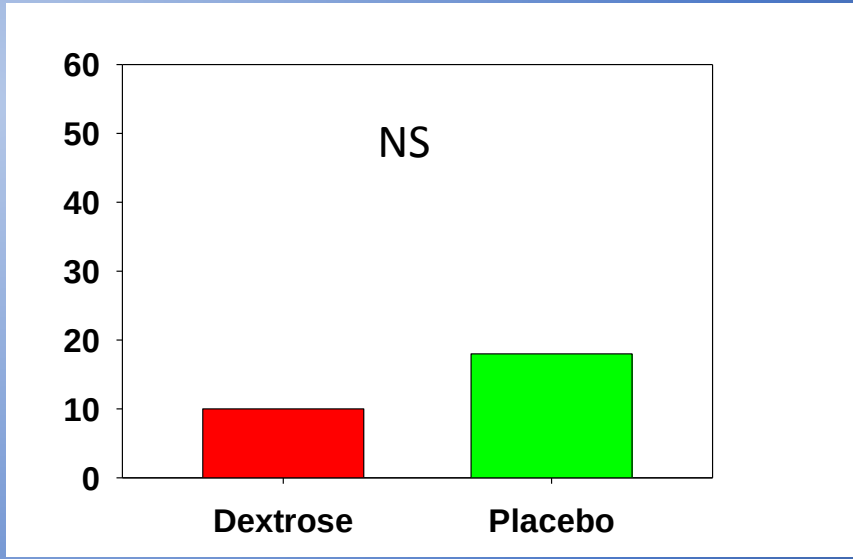
Outcome at 2 Years after Dextrose Gel Treatment for Neonatal Hypoglycemia: Follow-Up of a Randomized Trial

Deborah L. Harris, PhD[1,2], Jane M. Alsweiler, FRACP, PhD[2], Judith M. Ansell, PhD[2], Gregory D. Gamble, MSc[2], Benjamin Thompson, PhD[3], Trecia A. Wouldes, PhD[4], Tzu-Ying Yu, PhD[3], and Jane E. Harding, FRACP, D Phil[2], on behalf of the Children with Hypoglycaemia and their Later Development (CHYLD) Study Team*

% Neurosensory Impairment



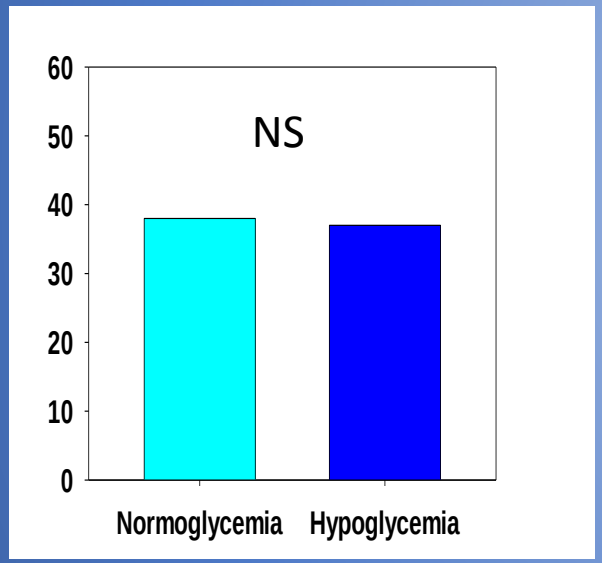
% Processing Difficulty



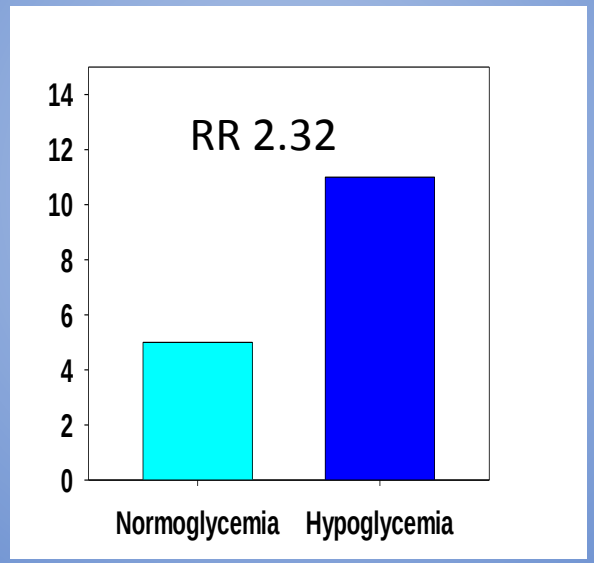
J Pediatr 2016; 170:54-9

Association of Neonatal Glycemia with Neurodevelopmental Outcomes at 4.5 Years

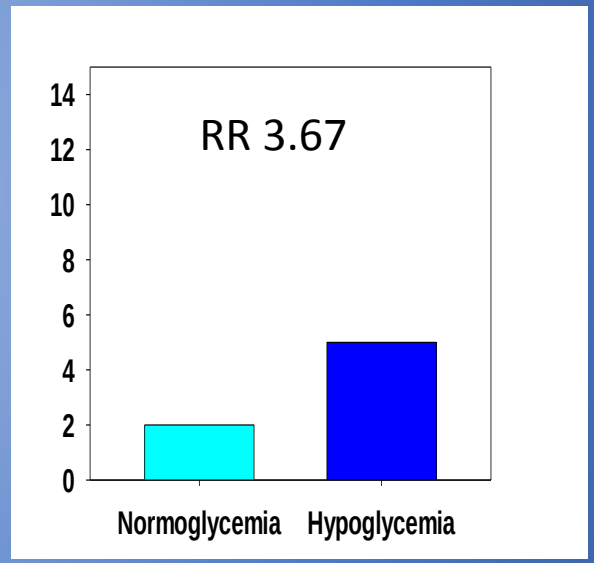
Neurosensory Impairment



Executive Function Difficulty



Visual-motor Integration Problem



Neonatal hypoglycemia was associated with a dose-dependent increased risk of poor executive function and visual motor function at 4.5 years, may influence later learning

PennState Health Children's Hospital

JAMA Pediatr 2017;171(10):972-83

Other Hypoglycemia Development Studies (Observational)

- Lucas, et al (1988): PT <1850 g, n=661, ≤45 mg/dL on ≥3 days, lower 18 month Bayley scores
- Brand, et al (2005): Healthy Term LGA, <40 mg/dL at 1 hour and <45 mg/dL thereafter, n=75, no difference on 4 year IQ test
- Tin, et al (2012): <32 weeks, n=76, ≤45 mg/dL on ≥3 days, no difference in 15 year IQ

BMJ 1988;297:1304-8; *Arch Dis Child* 2005;90:78-81; *Pediatrics* 2012;130:e1497-503

Bottom Line

- Eminence-based recommendations from the Pediatric Endocrine Society **(50 mg/dL)**

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- Our retrospective study **(45 mg/dL)**

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- Prospective Sugar Babies study **(47 mg/dL)**

Bottom Line (Opinion)

- Eminence-based recommendations from the Pediatric Endocrine Society **(50 mg/dL)**
- Our retrospective study **(45 mg/dL)**
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- **Opinion: Maintain newborn glucose concentrations >45-50 mg/dL**

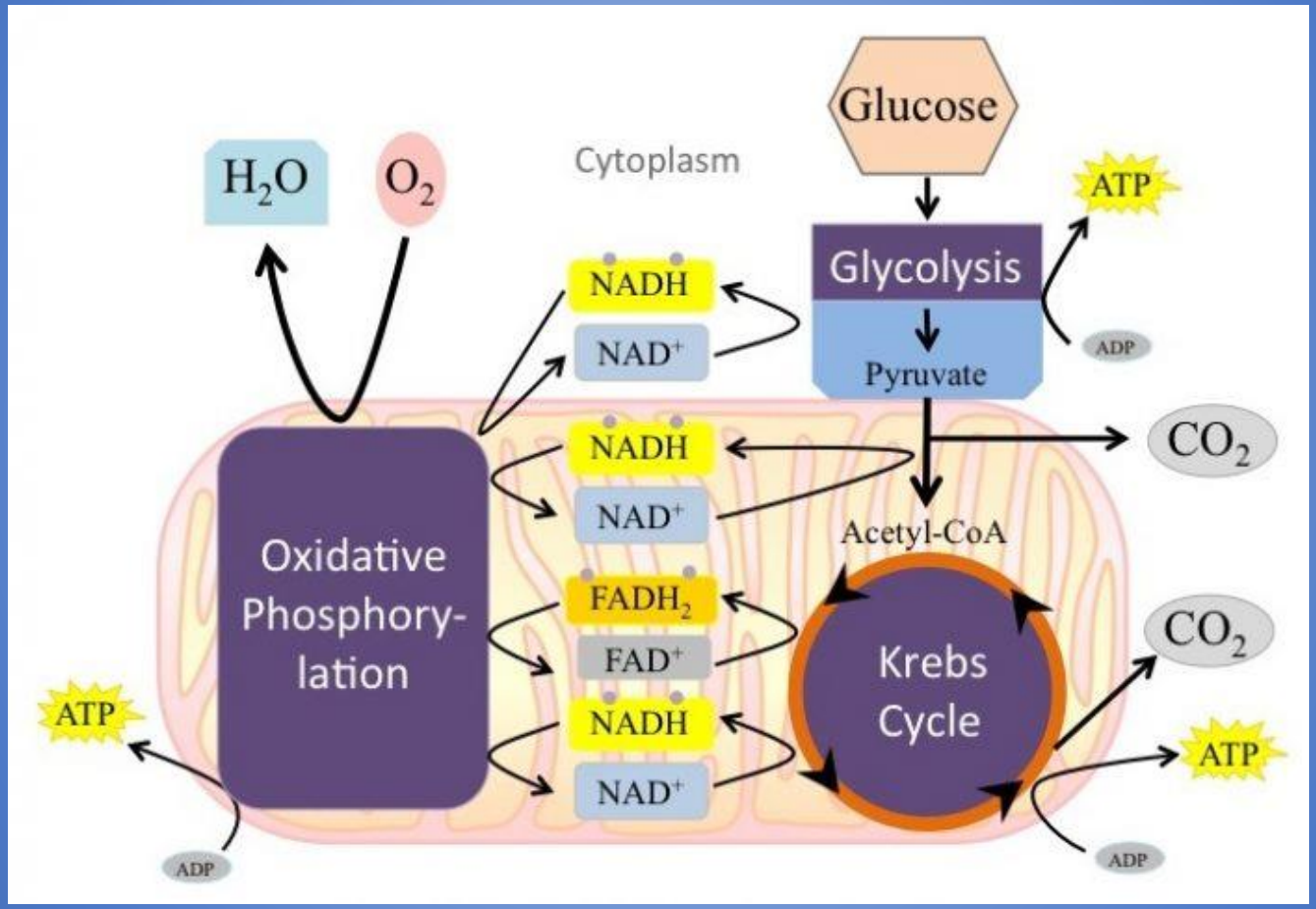
Bottom Line (Opinion)

- Eminence-based recommendations from the Pediatric Endocrine Society **(50 mg/dL)**
- Our retrospective study **(45 mg/dL)**
- Prospective Sugar Babies study **(47 mg/dL)**
- **Opinion: Maintain newborn glucose concentrations >45-50 mg/dL**
- **"opinion is the medium between knowledge and ignorance"--*Plato***

Proposed Randomized Controlled Trial for the Treatment of Asymptomatic Transient Neonatal Hypoglycemia

- During the first 48 hours, at-risk newborns will be randomized to the AAP vs PES treatment guidelines
- Treatment will be with 40% dextrose gel
- 1^{o} outcome: Executive Function, Visual-Motor Integration, and IQ at 3 years (and then at school age)
- RO1 application to be resubmitted
- **Please contact me with any ideas**

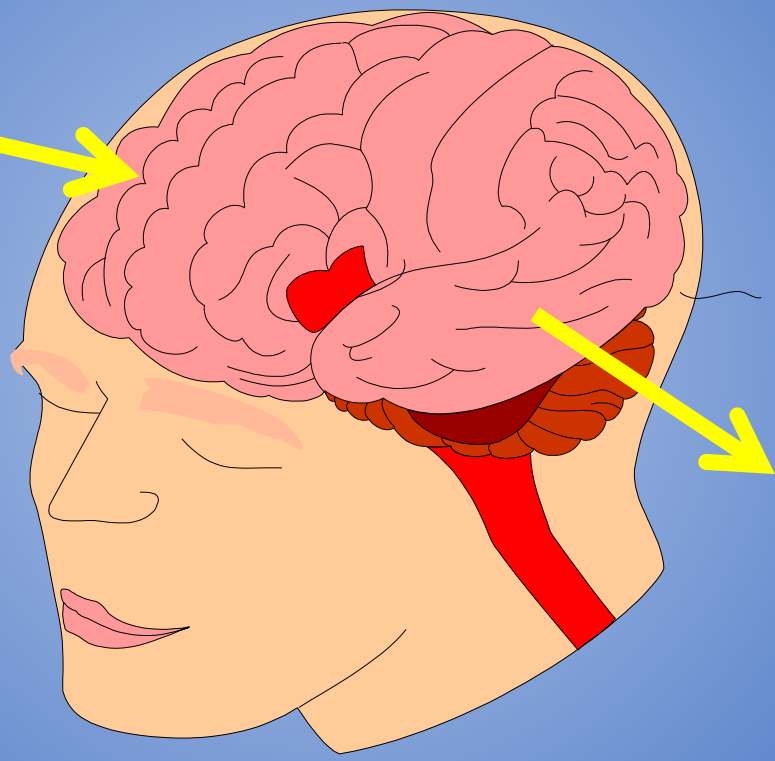
HIE and Glucose and PCO_2



Cellular Metabolism

Glucose

O_2



ATP

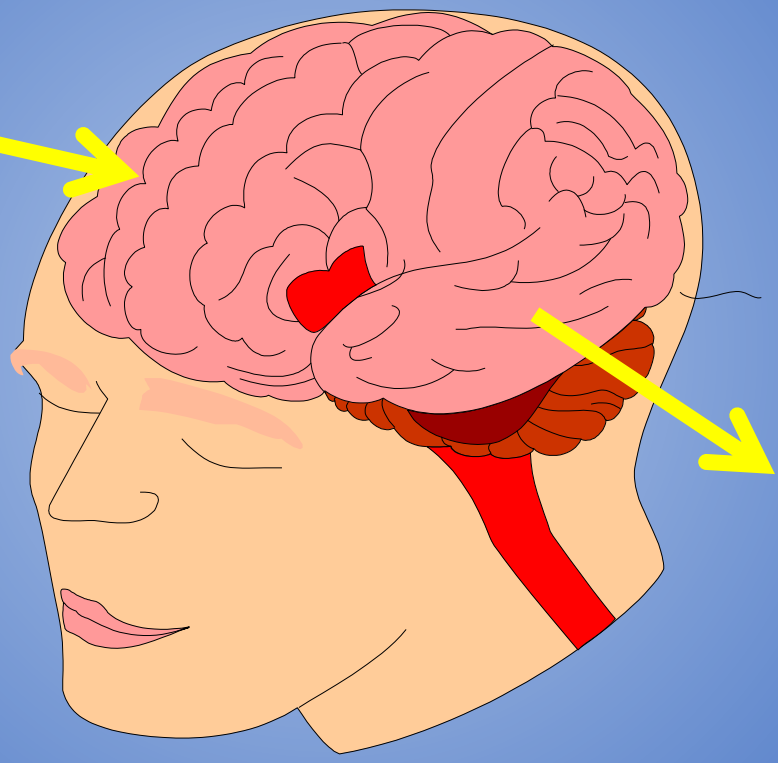
CO_2

H_2O

Cellular Metabolism

Glucose

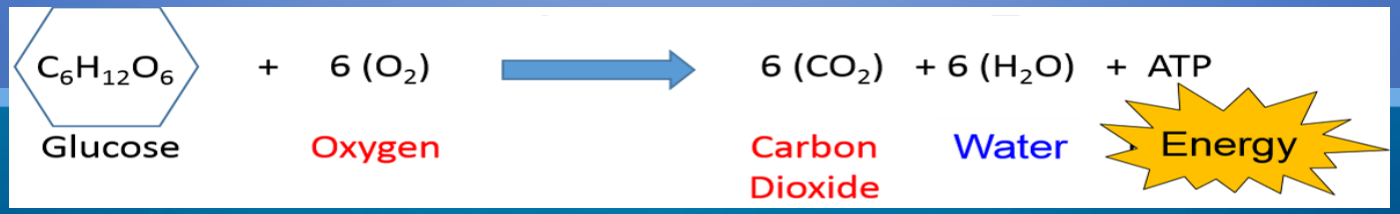
O_2



ATP

CO_2

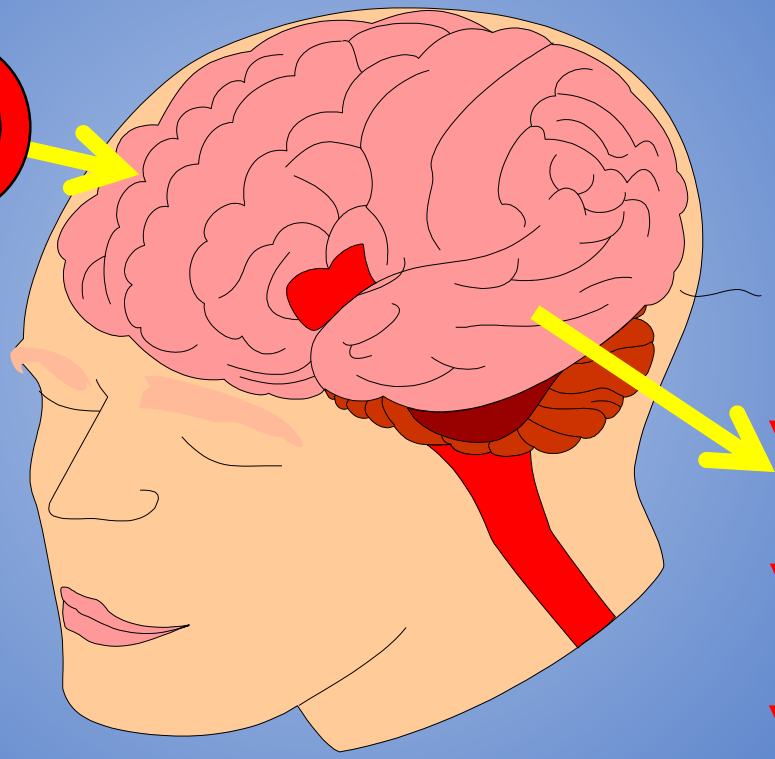
H_2O



Hypoxic Ischemic Brain Injury

Glucose

O_2



↓ATP

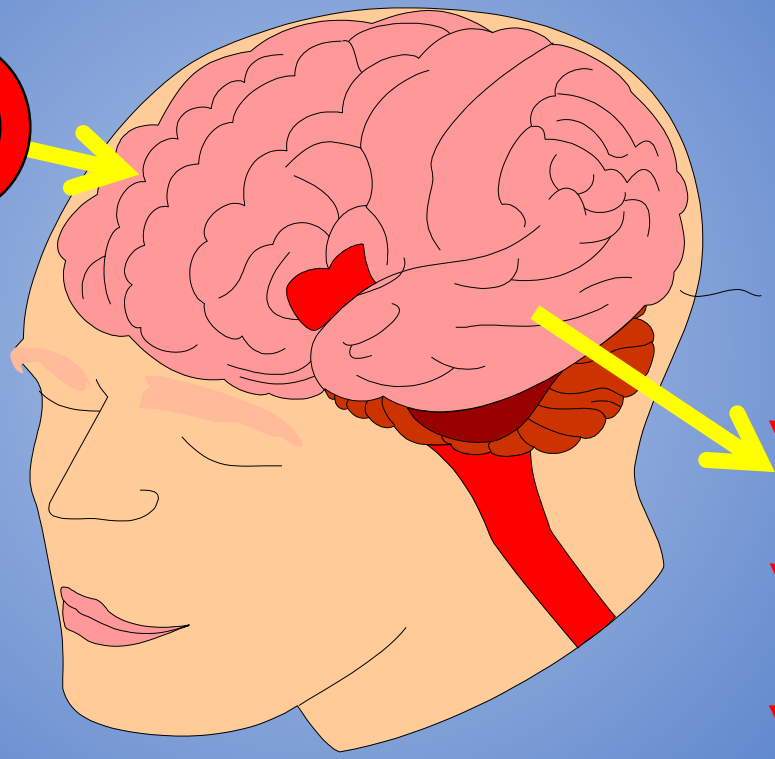
↓CO_2

↓H_2O

Hypoxic Ischemic Brain Injury

Glucose

O_2



↓ATP

↓CO_2

↓H_2O

↑Lactate

Glycemic Profile in Infants with HIE

HIE

Multi-organ failure

Liver injury

Depletion of glycogen stores

↓ Gluconeogenesis

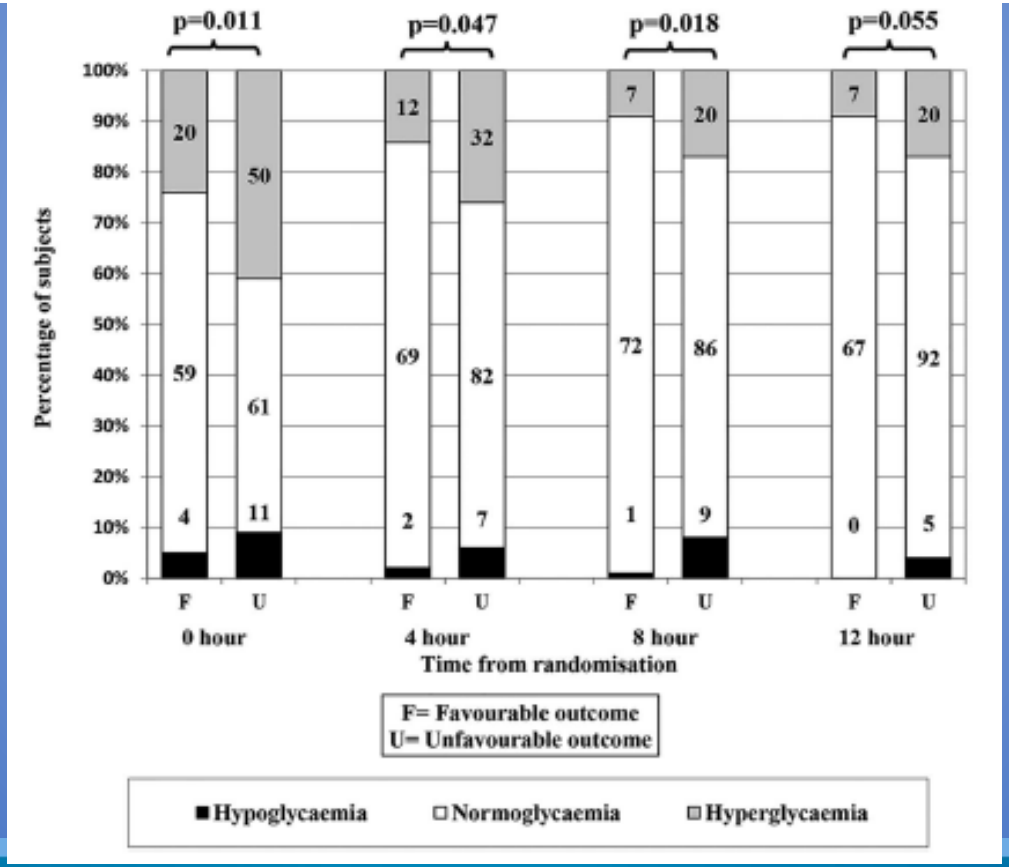
Hypoglycemia

With acute brain injury, damaged brain tissue has decreased metabolism

Hyperglycemia

Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study

Hypoglycemia is associated with 6.2 increased risk of unfavorable outcome



Hyperglycemia is associated with 2.7 increased risk of unfavorable outcome

PennState Health Children's Hospital

Basu et al. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F149-55

Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study

Table 3 Effect of hypothermia therapy on risk of death and/or severe neurological disability at 18 months

	Rate of primary outcome		Relative difference* in risk		Absolute difference* in risk		
Group	Cooled n/total (%)	Not cooled n/total (%)	Unadjusted RR (95% CI)	aRR (95% CI)	Unadjusted RD (95% CI)	aRD (95% CI)	NNT†
Overall	54/99 (55)	64/95 (67)	0.81 (0.64 to 1.02)	0.77 (0.63 to 0.94)	−13% (−26% to 1%)	−16% (−28% to −3%)	7
12-hour Glucose profile							
Normoglycaemia	23/47 (49)	21/42 (50)	0.98 (0.64 to 1.49)	0.95 (0.70 to 1.27)	−1% (−22% to 20%)	−5% (−26% to 16%)	100
Hypoglycaemia	4/5 (80)	11/13 (85)	0.95 (0.58 to 1.55)	1.03 (0.52 to 2.00)	−5% (−45% to 36%)	1% (−53% to 55%)	n/a
Hyperglycaemia	27/47 (58)	32/40 (80)	0.72 (0.54 to 0.96)	0.80 (0.66 to 0.99)	−23% (−41% to −4%)	−22% (−39% to −4%)	5

*The reference group consists of infants that are 'not cooled' for all relative risk and RD models.
†The NNT is calculated from the aRD point estimate and presents the number of infants that would have to be cooled in order to prevent one unfavourable 18-month outcome. The NNT is rounded to the next highest whole integer. The NNT is not estimated for the hypoglycaemia group since the point estimate does not reflect a risk reduction conferred by hypothermia therapy.
aRD, adjusted risk difference; aRR, adjusted risk ratio; NNT, number needed to treat.

Basu et al. *Arch Dis Child Neonatal Fetal Ed* 2017;102(4):F299-306

Hyperglycaemia in infants with hypoxic–ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study

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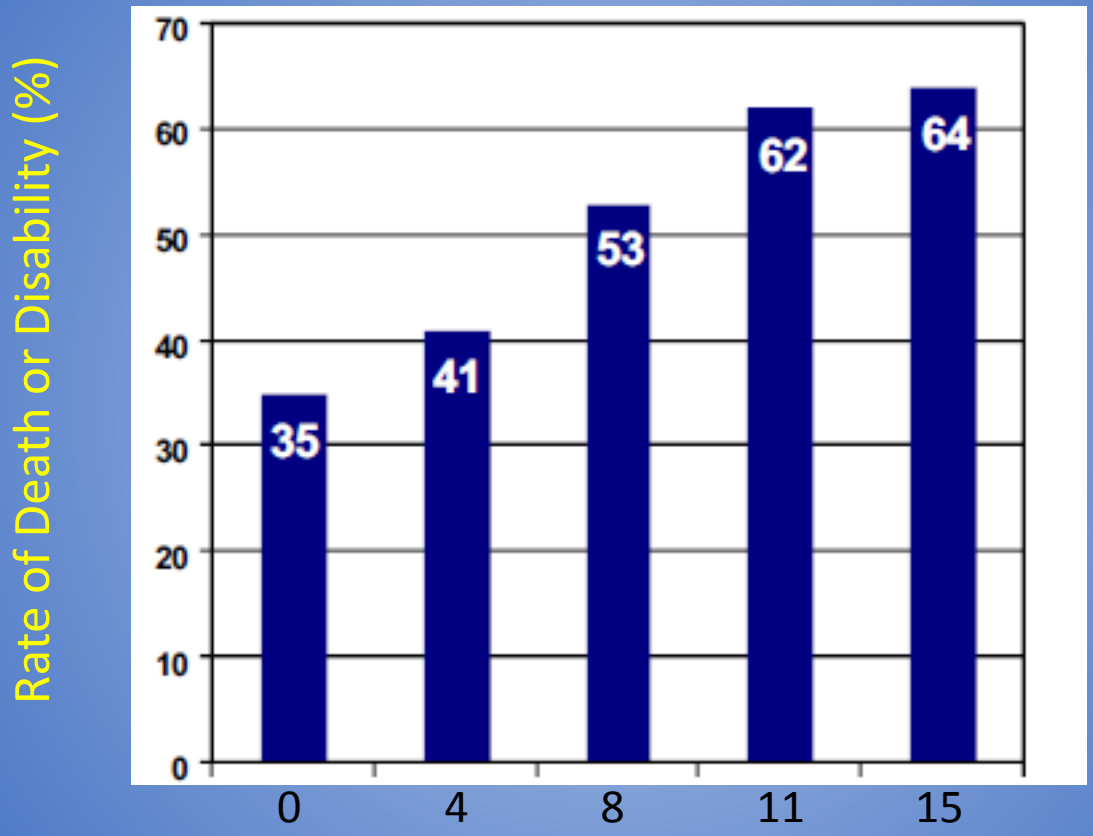
aRD, adjusted risk difference; aRR, adjusted risk ratio; NNT, number needed to treat.

Basu et al. *Arch Dis Child Neonatal Fetal Ed* 2017;102(4):F299-306

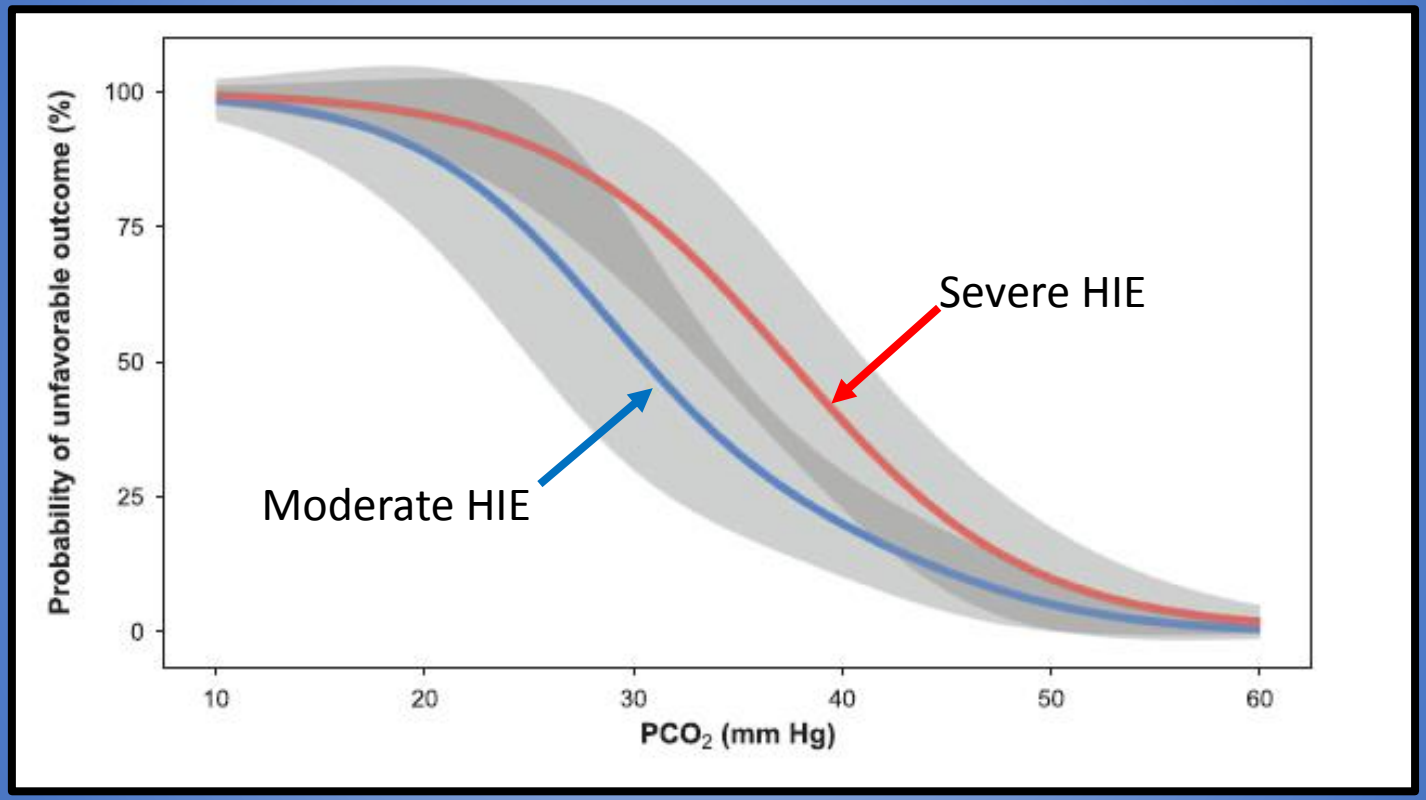
Rate of Death and/or Disability in Infants with HIE is Increased with Greater Exposure to Hypocapnia



Pappas, et al. *J Pediatr* 2011;158:752-8

Lower PCO_2 is Newborns with HIE is Associated with Unfavorable Outcomes

Bad Outcome ⟶

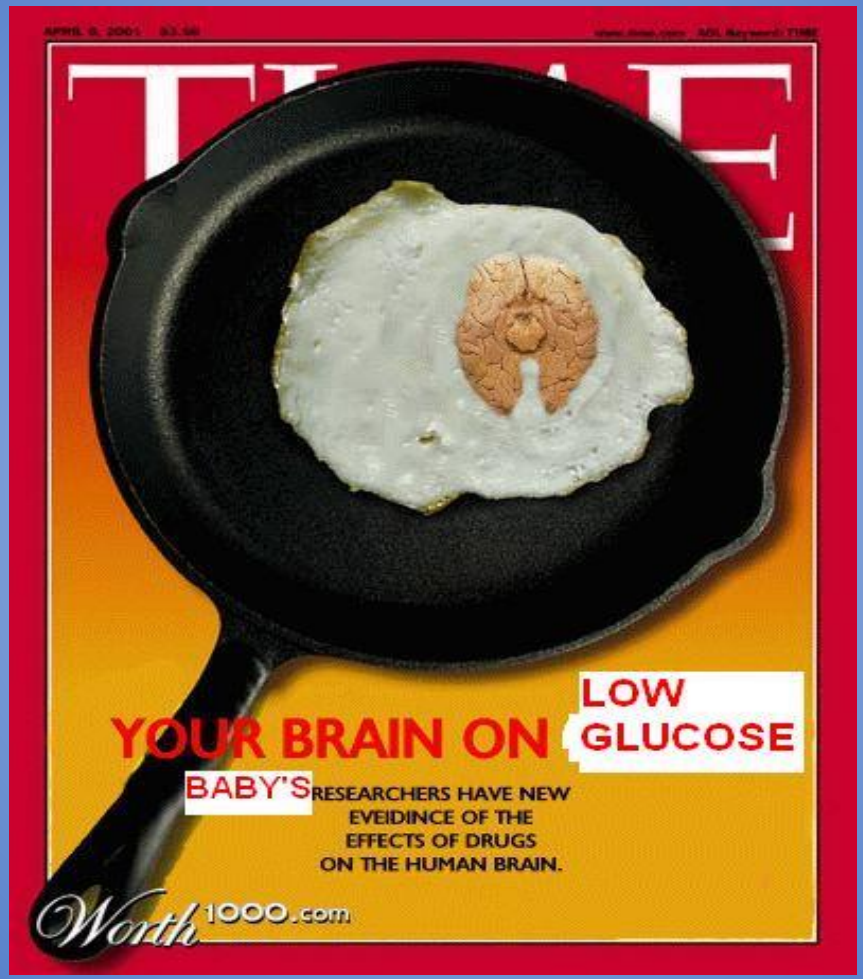


PCO_2 ⟶

Lingappan et al. *Pediatr Res* 2016;80:204-8

This is Your Baby's Brain

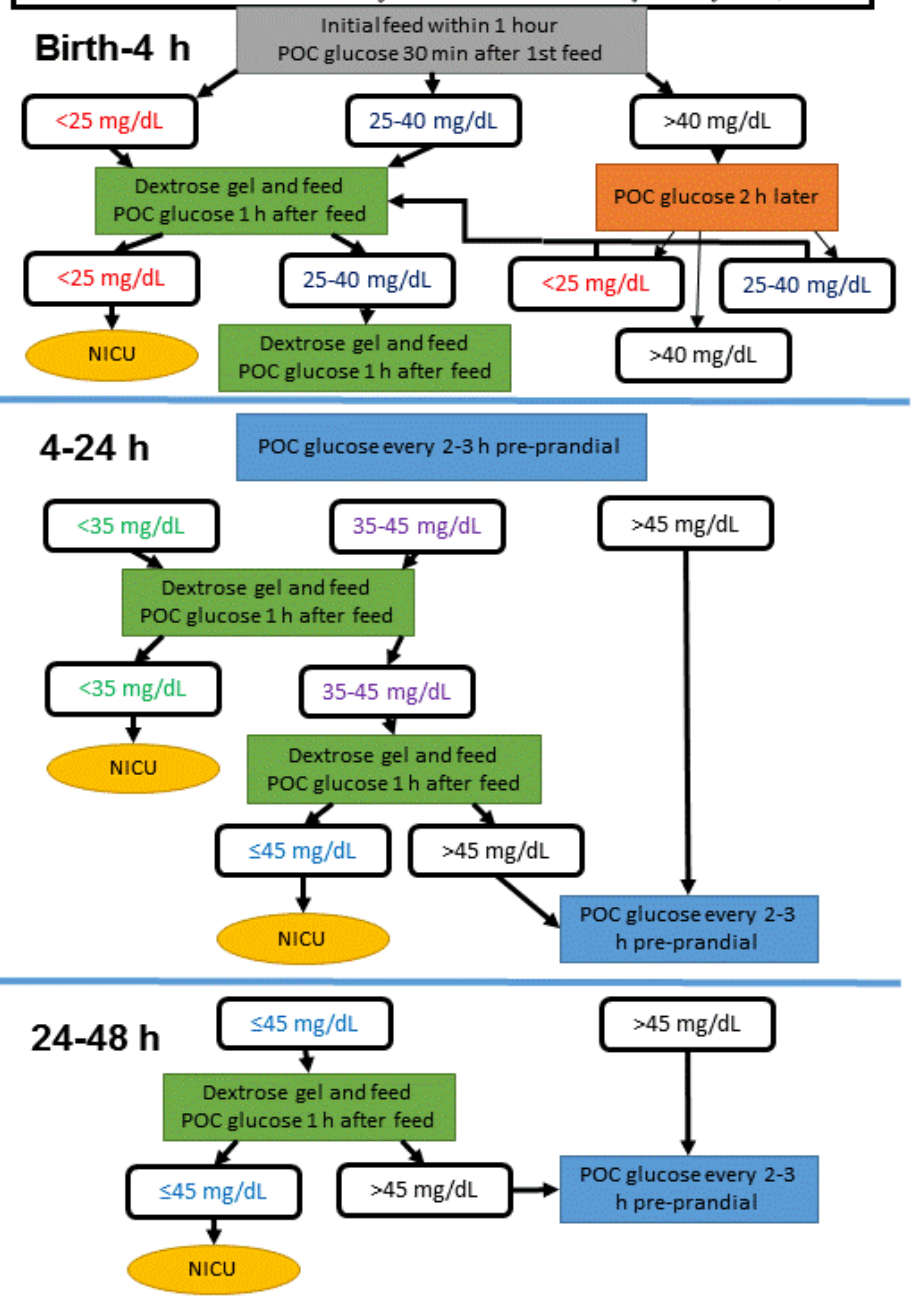
This is Your Baby's Brain on Low Glucose



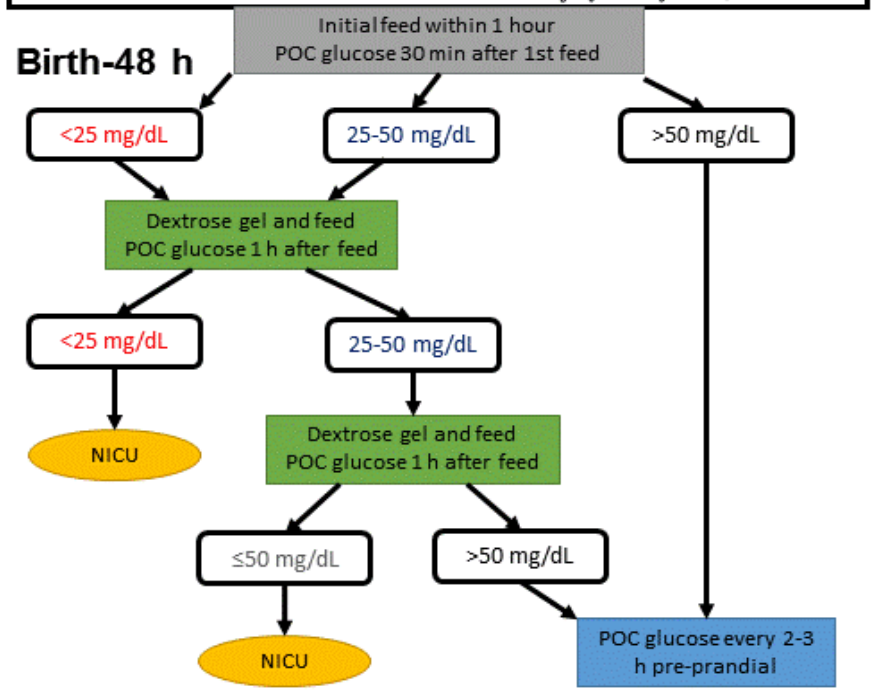

ANY
QUESTIONS
?

ASYMPTOMATIC

American Academy of Pediatrics (AAP)-Adapted



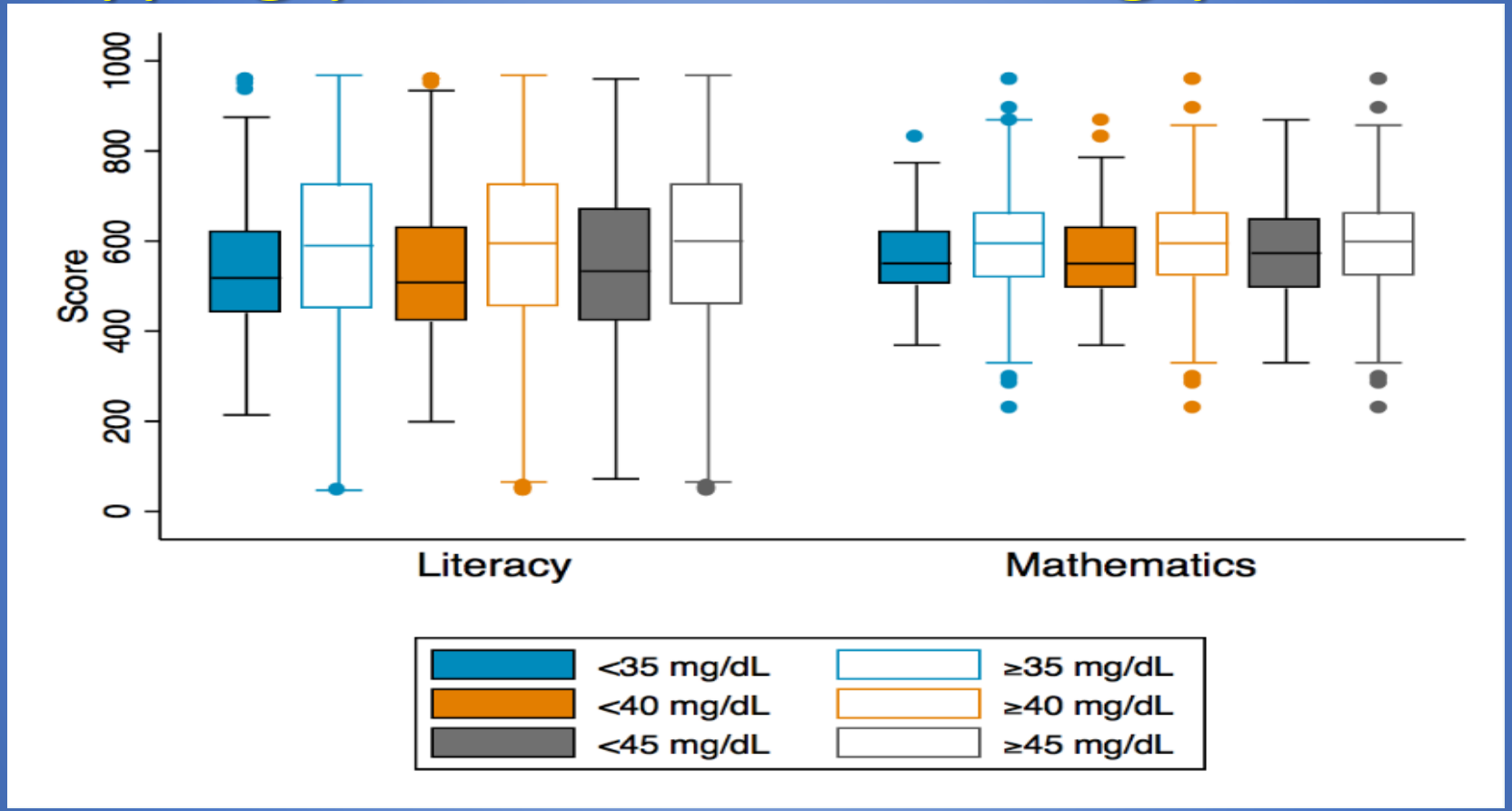
Pediatric Endocrine Society (PES)-Adapted



Management of asymptomatic at risk-newborns: 35-36 weeks, IDMs, SGA, and LGA using AAP vs PES Guidelines

- Feed: breastfeeding, donor breastmilk, or formula
- POC glucose: use Nova Biomedical StatStrip
- Dextrose gel: 0.5 ml/kg massaged into left and right buccal mucosa
- AAP: If newborn has POC glucose >45 mg/dL (4-48 h) and follow-up value is ≤45 mg/dL, then return to age-based algorithm for management; if remains low, admit to the NICU
- PES: If newborn has POC glucose >50 mg/dL (Birth-48 h) and follow-up value is ≤50 mg/dL, return to algorithm for management; if remains low, admit to the NICU
- May give up to 3 doses of dextrose gel

Achievement Test Scores for Hypoglycemic and Normoglycemic



Unadjusted

JAMA Pediatr 2015; 169:913-21

Comparison of Neurodevelopmental Studies

	Lucas	Brand	Tin
Year	1988 (early '80s)	2005 ('97-98)	2012 ('90-91)
Multicenter	Yes, 5	No	Yes, 13
Population	LBW <1850 g	Healthy term LGA	<32 weeks
N	661	75	566
Age at FU	1.5 years	4 years	15 years
% FU	92%	64%	81%
Hypoglycemia defn	≤45 mg/dL on ≥3 days	<40 at 1 hr, <45 mg/dL after	≤45 mg/dL on ≥3 days
N (%) hypoglycemic	104 (16%)	60 (80%)	47 (8%)
Plasma glucose	Lab (plasma)	? (blood glucose)/plasma	Lab (blood glucose)
Duration of monitoring	9 weeks	DOL #1	10 days
Pre-set sampling	No	Yes	Yes
Prospective data collection	Yes	Yes	Yes
Study design	Prospective observational	Prospective	Prospective case-control
Adjusted for SES/Mat Ed	Yes	No	No
Tests	Bayley	Denver, Behavior, IQ	IQ
Hypoglycemia: poor outcome	Yes	No	No

BMJ 1988;297:1304-8

Comparison of Neurodevelopmental Studies

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Arch Dis Child 2005;90:78-81

Comparison of Neurodevelopmental Studies

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Adjusted for SES/Mat Ed	Yes	No	No
Tests	Bayley	Denver, Behavior, IQ	IQ
Hypoglycemia: poor outcome	Yes	No	No

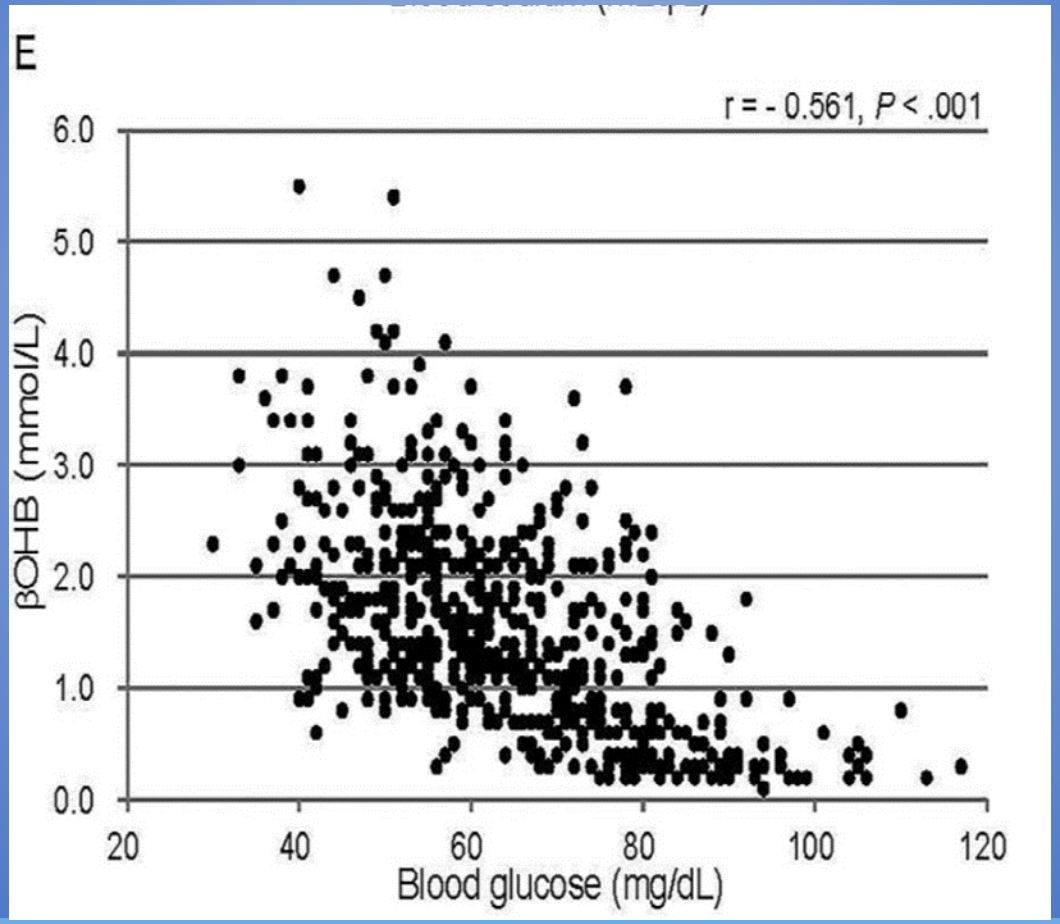
Pediatrics 2012;130:e1497-503

Comparison of Neurodevelopmental Studies

	Lucas	Brand	Tin	Kaiser
Year	1988 (early '80s)	2005 ('97-98)	2012 ('90-91)	2015 ('98)
Multicenter	Yes, 5	No	Yes, 13	No
Population	LBW <1850 g	Healthy term LGA	<32 weeks	23-42 weeks
N	661	75	566	1395
Age at FU	1.5 years	4 years	15 years	10 years
% FU	92%	64%	81%	72%
Hypoglycemia defn	≤45 mg/dL on ≥3 days	<40 at 1 hr, <45 mg/dL after	≤45 mg/dL on ≥3 days	<35, <40, <45 mg/dL
N (%) hypoglycemic	104 (16%)	60 (80%)	47 (8%)	89 (6.4%); 143 (10.3%); 269 (19.3%)
Plasma glucose	Lab (plasma)	? (blood glucose)/plasma	Lab (blood glucose)	Lab (plasma)
Duration of monitoring	9 weeks	DOL #1	10 days	3 hours
Pre-set sampling	No	Yes	Yes	Yes
Prospective data collection	Yes	Yes	Yes	No
Study design	Prospective observational	Prospective	Prospective case-control	Retrospective
Adjusted for SES/Mat Ed	Yes	No	No	Yes
Tests	Bayley	Denver, Behavior, IQ	IQ	Achievement tests
Hypoglycemia: poor outcome	Yes	No	No	**Yes**

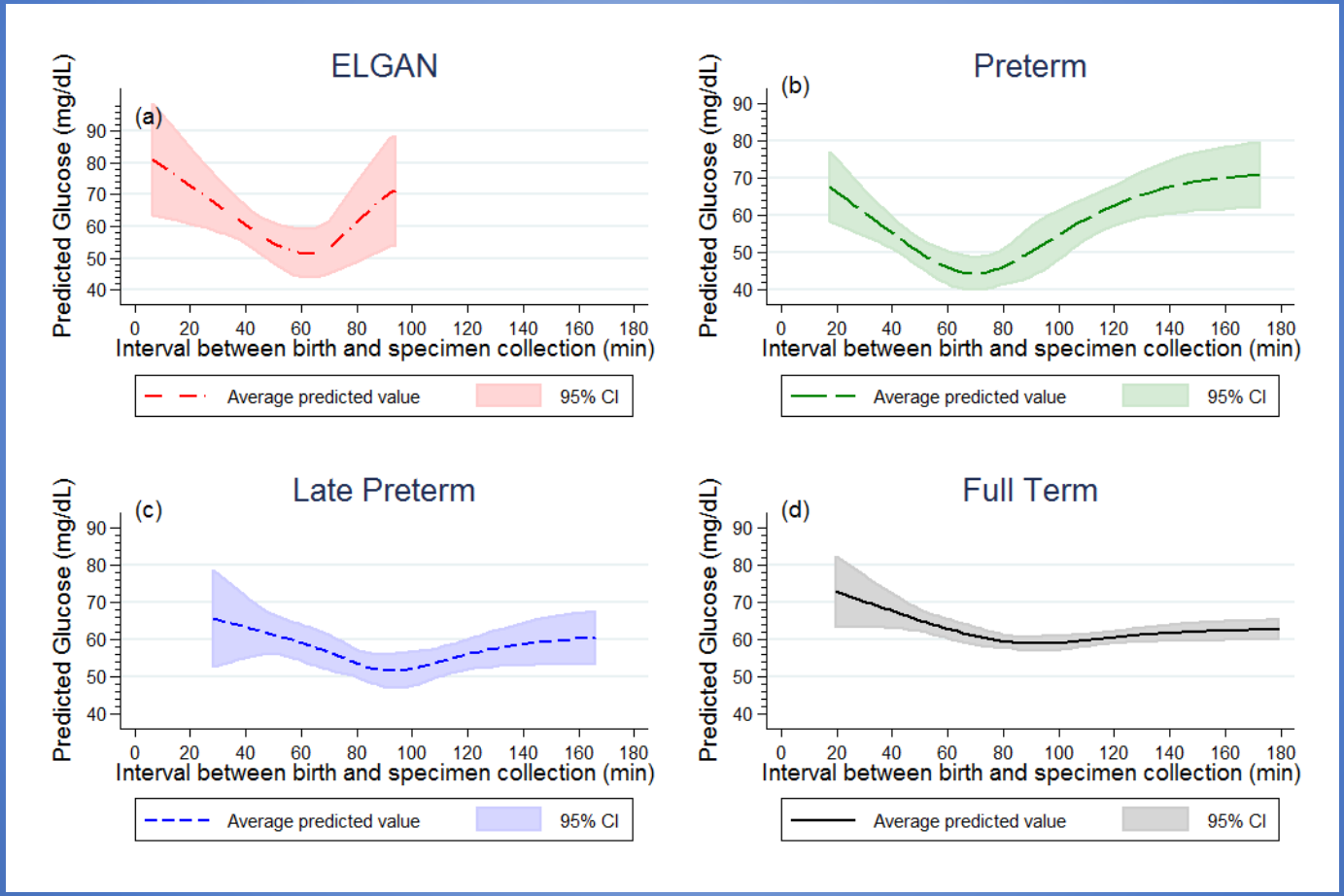
JAMA Pediatr 2015;169:913-21

Blood Ketones After 48 Hours of Age in Breastfed Infants and the Relationship to Glucose Concentrations

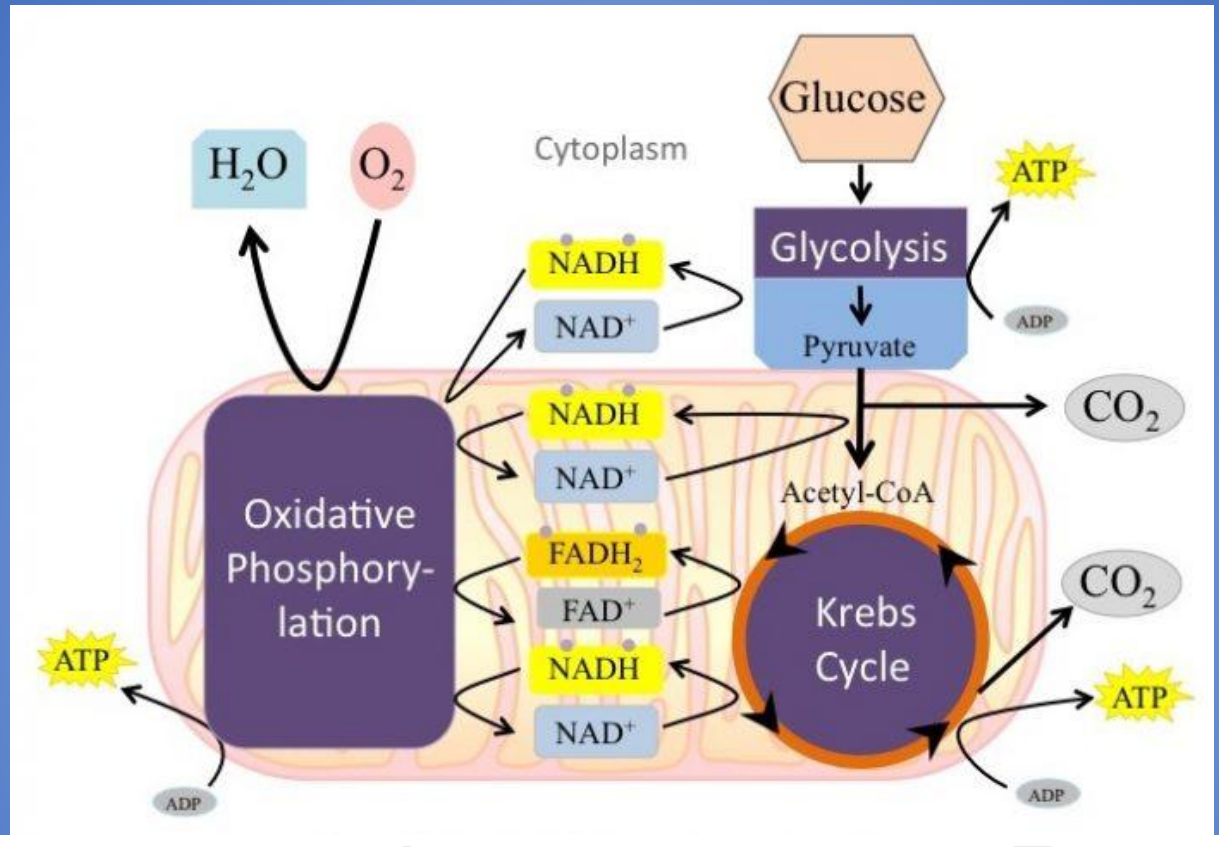


Futatani et al. *J Pediatr* 2017;191:76-81

Pattern of Glucose Concentrations for ELGAN, PT, LPT, and FT Newborns with 95% CI



Aerobic Cellular Respiration



$C_6H_{12}O_6$ + 6 (O_2) → 6 (CO_2) + 6 (H_2O) + ATP

Glucose — Oxygen — Carbon Dioxide — Water — Energy