Neonatal Hypoglycemia

Presented by
Paul J. Rozance, MD
Frederick C. Battaglia Endowed Chair in Neonatology
Children's Hospital Colorado
Professor, Department of Pediatrics
Perinatal Research Center
University of Colorado School of Medicine
Aurora, Colorado

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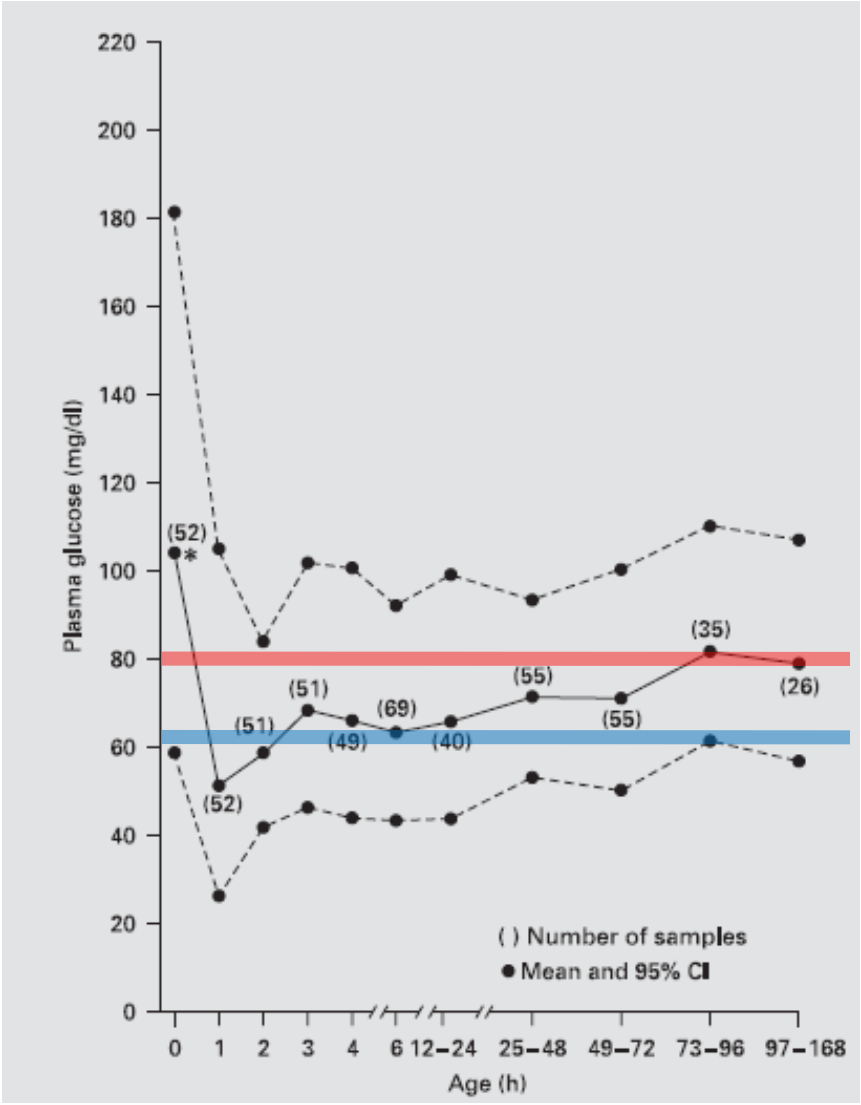
Learning Objectives

At the conclusion of this module, participants should be better able to:

- Treat asymptomatic neonatal hypoglycemia with buccal dextrose gel
- Develop patient-specific approaches to intravenous dextrose therapy for neonatal hypoglycemia

Fetal Glucose Concentrations Normally Persist for Up to 48 Hours After Birth and Then Transition to Adult Concentrations



Maternal Glucose Concentrations

Fetal Glucose Concentrations

Marconi, 1996
Srinivasan, 1986

Common Complications of Pregnancy May Exaggerate and Prolong This Transitional Physiology

- The main at risk groups:
  - Placental insufficiency (IUGR/SGA)
  - Diabetes during pregnancy and other causes of fetal over nutrition (IDM, LGA)
  - Prenatal and perinatal stress
  - Late preterm delivery
- All of these complications impact fetal glucose metabolism and the transition to postnatal glucose metabolism.
- They all impact neonatal glucose concentrations.

Why Do We Care About Asymptomatic Hypoglycemia?

- Early diagnosis and treatment of severe genetic and/or congenital hypoglycemia disorders
  - Persistent Congenital Hyperinsulinism - (1:40,000)
  - Fatty Acid Oxidation Disorders (and other metabolic defects) - (1:10,000-15,000)
  - Hypopituitarism - (1:20,000)
- Progression to symptomatic hypoglycemia
  - Associative data
- Persistent asymptomatic hypoglycemia
  - Associative and Controversial !!!!!!

Outcome Data in the Main At-Risk Groups

- There are studies in most of the main at-risk groups which show worse outcomes than healthy term newborns.
- In some of these studies an association exists between low glucose concentrations and worse neurodevelopmental outcomes.
- No studies have robustly tested whether treating asymptomatic hypoglycemia improves neurodevelopmental outcomes.

AAP Guidelines 2011

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

[(LPT) Infants 34 – $36^{6/7}$ weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)]

Symptomatic and <40 mg/dL ⟶ IV glucose

ASYMPTOMATIC

Birth to 4 hours of age		4 to 24 hours of age	
INITIAL FEED WITHIN 1 hour Screen glucose 30 minutes after 1st feed		Continue feeds q 2-3 hours Screen glucose prior to each feed	
Initial screen <25 mg/dL		Screen <35 mg/dL	
Feed and check in 1 hour		Feed and check in 1 hour	
<25 mg/dL ↓ IV glucose*	25–40 mg/dL ↓ Refeed/IV glucose* as needed	<35 mg/dL ↓ IV glucose*	35 – 45 mg/dL ↓ Refeed/IV glucose* as needed

Target glucose screen ≥45 mg/dL prior to routine feeds

* Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Gaps and Controversies in the AAP Statement

- Symptomatic infants without risk factors
- Other high risk groups
- How to manage beyond the first 24 hours
  - When and how to consider a hypoglycemic disorder
  - Other biochemical studies
  - How to determine safety for discharge
- Why are there gaps and controversies in the AAP Statement?
  - Any protocol that is specific enough to be useful will create controversy

Pediatric Endocrine Society Recommendations 2015

MEDICAL PROGRESS

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

Paul S. Thornton, MB, BCh[1], Charles A. Stanley, MD[2], Diva D. De Leon, MD, MSCE[2], Deborah Harris, PhD[3], Morey W. Haymond, MD[4], Khalid Hussain, MD, MPH[5], Lynne L. Levitsky, MD[6], Mohammad H. Murad, MD, MPH[7], Paul J. Rozance, MD[8], Rebecca A. Simmons, MD[9], Mark A. Sperling, MBBS[10], David A. Weinstein, MD, MMSc[11], Neil H. White, MD[12], and Joseph I. Wolfsdorf, MB, BCh[13]

AAP vs PES

Key Differences

- What glucose concentrations to use for treatment targets.
- Who and how to investigate for a hypoglycemia disorder.
- When to obtain critical labs and what critical labs should be obtained.
- Is the patient ready for discharge.

AAP vs PES

When to use which guideline?

- AAP – “Screening and management…”
  - Screening at-risk asymptomatic newborns
  - Management in the first 24-48 hours
- PES – “…evaluation and management…”
  - Management
    - Other groups of patients
    - Especially after 48 hours
    - Discharge
  - Diagnosis

So What Is One to Do?

One Person's Practical Approach

- For the first 24 hours of life use the AAP guidelines.
  - If the baby requires IV dextrose, use the PES guidelines for treatment goals.
- For hours 24-48 use either AAP or PES guidelines mg/dL as treatment targets (>40-50 mg/dL vs >50 mg/dL)
- For >48 hours of age use PES guidelines.
  - Once the patient has transitioned to a "dextrose weaning phase" accept glucose concentrations >50 mg/dL.
- For symptomatic patients, especially without risk factors, use the PES guidelines.
- For discharge use PES guidelines.*

Approach to Discharge

- Patient specific
- Safety fasting test skip one feed
  - Hypoglycemia with:
    - Neurological signs
    - No known risk factors, but needed intravenous dextrose
    - Family history of sudden infant death of unknown cause in a sibling
    - Physical exam consistent with a congenital disorder associated with hypoglycemia (Beckwith-Wiedemann, hypopituitarism)
    - Inability to consistently maintain plasma glucose above 60 mg/dL.
  - Family history of a chronic hypoglycemia disorder (in consultation with an endocrinologist)

The “Minimum” or “Safety” Fasting Study

- 3-4 hours after the last feed begin checking glucoses
- Use a rapid “blood gas analyzer” if available or a highly accurate bedside glucometer
  - If it is not available consider using 40 mg/dL as a cut-off
- When glucose is <50mg/dL (consider 40 mg/dL if using a glucometer) immediately draw:
  - Glucose, insulin, beta-hydroxybutyrate, cortisol, growth hormone
- Feed after labs are drawn
- If patient is >60-65 mg/dL after 6 hours it is probably OK to stop and feed the patient
- If 50-60 mg/dL consider extending to 9 hours and if patient is >50 mg/dL it is probably OK to stop and feed the patient

Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years

McKinlay CJD, et al. *N Engl J Med.* 2015;373:1507-1518.

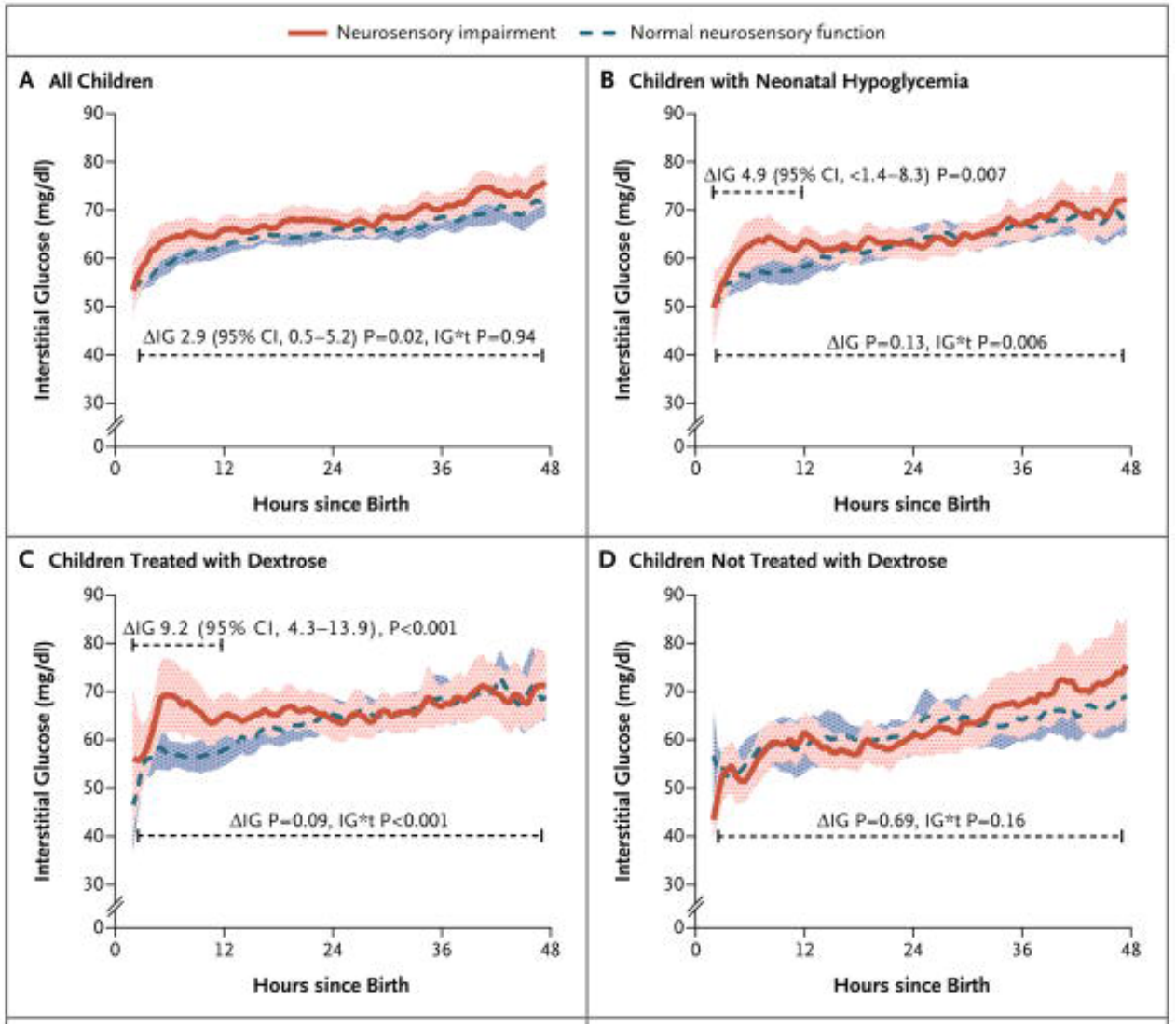
- At-risk groups for asymptomatic hypoglycemia
  - SGA, LGA, IDM, Late preterm (>35 weeks)
- Definition of hypoglycemia and treatment goal
  - 47 mg/dL
- Screening frequency
  - Before each feed for up to 48 hours
- Hypoglycemic babies had similar outcomes as normoglycemic babies at 2 years.

Three Associations

1. Those who did not have glucose lower than 54 mg/dL did worse than those who did.
   - By CGMS those with worse outcomes had a glucose concentration that was 2.9 mg/dL higher on average.
2. Of hypoglycemic infants, those with worse outcomes had a steeper rise in their glucose concentrations after treatment with dextrose.
3. Infants who had more time with glucoses outside the range of 54-72 mg/dL did worse.
   - Glycemic variability

McKinlay CJD, et al. *N Engl J Med*. 2015;373:1507-1518.

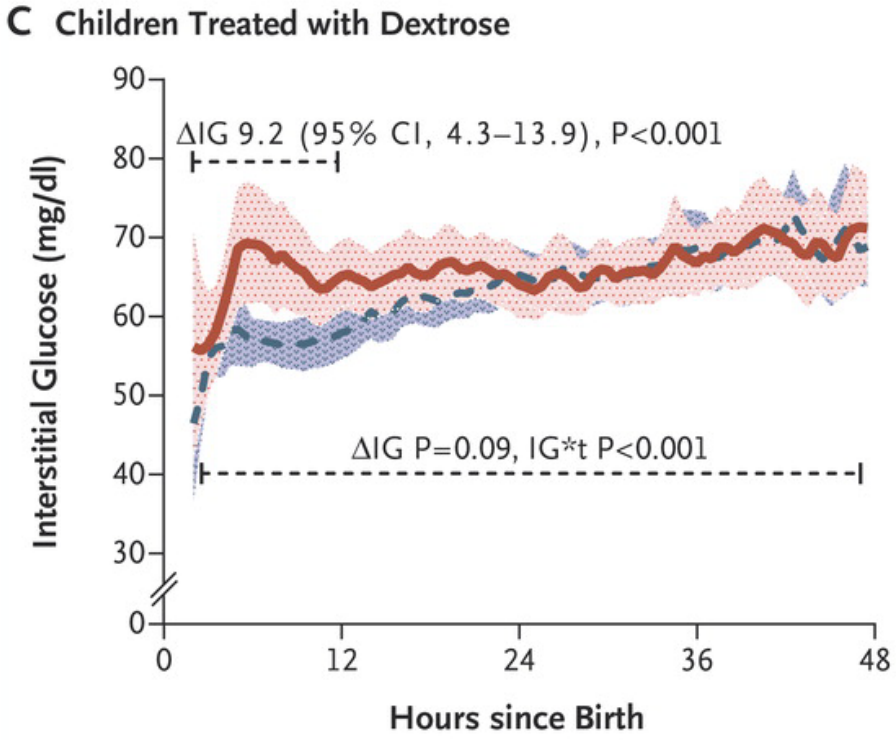
A More Rapid Rise After Treatment Was Associated With Worse Outcomes

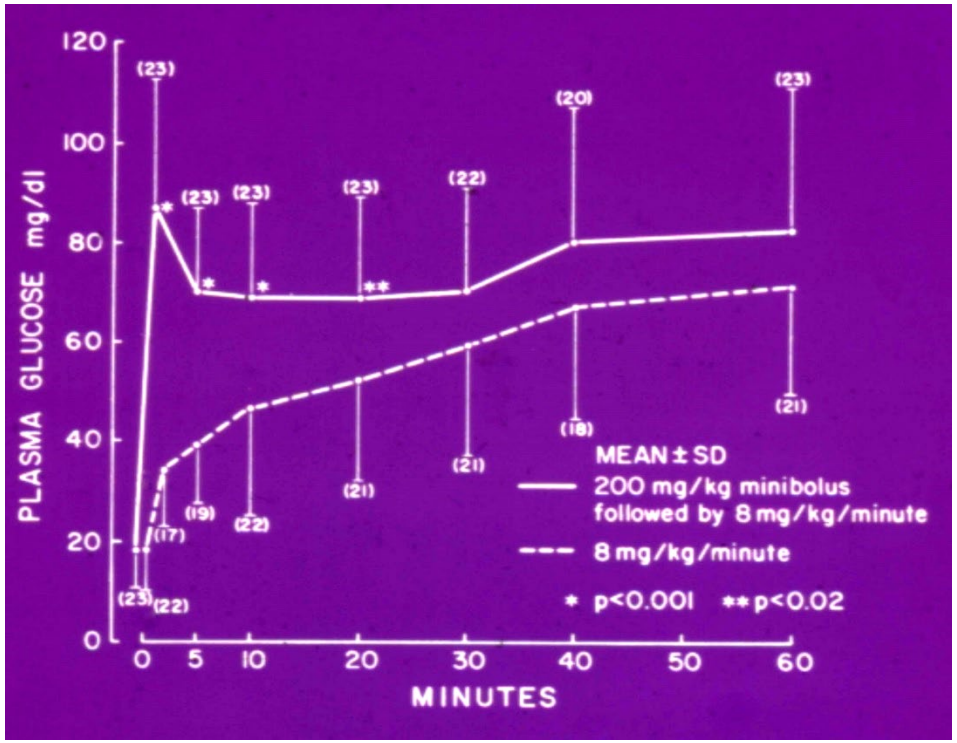


McKinlay CJD, et al. *N Engl J Med*. 2015; 373:1507-1518. Copyright 2015. Reproduced with permission from Massachusetts Medical Society.

Intravenous Treatment of Hypoglycemia:

Skip the 2 ml/kg D10W bolus for asymptomatic SGA, LGA, IDM, and late preterm newborns





Left: McKinlay CJD, et al. *N Engl J Med*. 2015; 373:1507-1518. Copyright 2015. Reproduced with permission from Massachusetts Medical Society.
Right: Lilien LD, et al. *J Pediatr.* 1980;97(2):295-8.

Neonatal Glycemia and Neurodevelopmental Outcomes at 4.5 Years

McKinlay CJD, et al. *JAMA Pediatr.* 2017;171(10):972-983.

- Hypoglycemic (<47 mg/dL) babies had worse executive function and worse visual motor function compared to normoglycemic babies at 2 years.
- There were not significant differences in parental assessment of their children.
- However, the poor executive function and visual motor performance may impact learning and school achievement.
- The other associations reported at 2 years of age were not reported at 4.5 years of age.

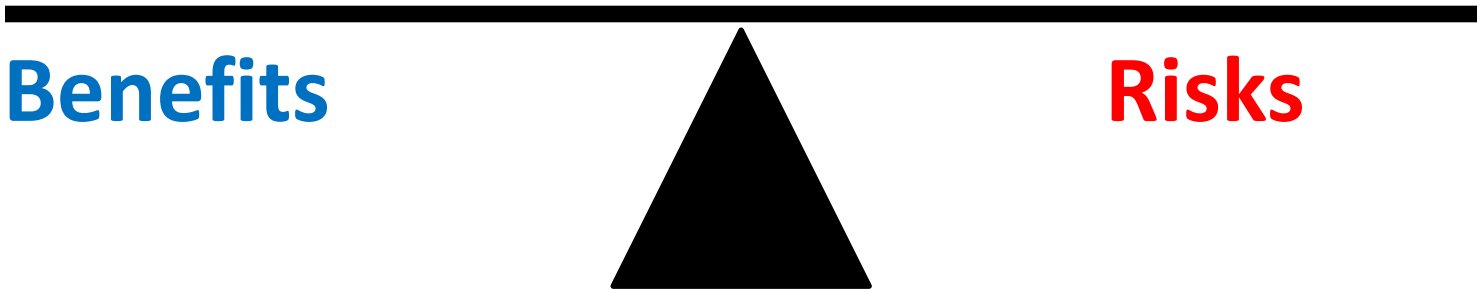
What Do These Studies Show?

- Using a screening and treatment strategy to actively increase glucose concentrations to >47 mg/dL, those with a glucose concentration <47 mg/dL:
  - Had equivalent outcomes at 2 years of age, but
  - Had worse outcomes at 4.5 years of age compared to patients that did not have a glucose concentration < 47 mg/dL
- They do not define one management strategy as better than another.
- Importance of longer term follow-up.

How Aggressively Do You Diagnose and Treat Hypoglycemia?

- Early treatment of severe hypoglycemia disorders
- Potential to prevent symptoms
- Potential to prevent neurological injury
- Correct an abnormality
- Less legal risk

- Separation from mother
- NICU admission
- Hospital stay and cost
- Decreased breast feeding
- Intravenous catheters
- Medication side effects
- Hyperglycemia

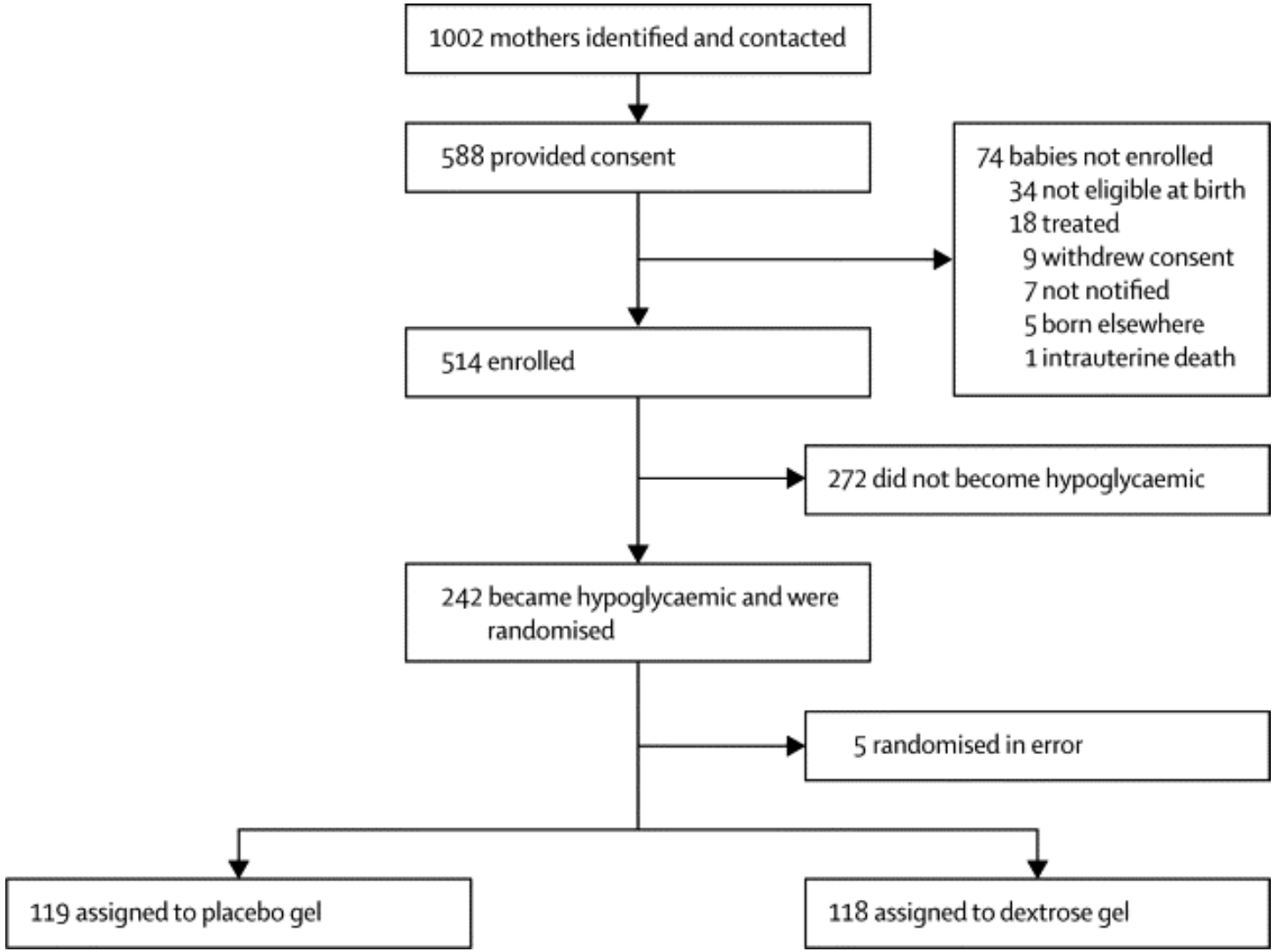


The Sugar Babies Study (Dextrose Gel)

- At risk groups - SGA, IDM, LGA, Late Preterm (>35 weeks)
- Plasma glucose measured before each feed for 48 hours
- Hypoglycemia defined as a plasma glucose ≤ 47 mg/dL
- Treated with dextrose gel or placebo gel (blinded) and feeds
  - When a low glucose concentrations was identified placebo gel or dextrose gel (200 mg/kg) was massaged into the buccal mucosa and the baby was encouraged to feed
  - The blood glucose concentrations was rechecked 30 minutes after gel administration
  - Primary endpoint: Treatment failure defined as a blood glucose concentration ≤ 47 mg/dL after the second of 2 doses of study gel
  - After 2 study gel doses the clinicians could use open label dextrose gel
  - Up to 6 total doses of gel (study + open label) could be give over a 48 hour period
  - Rebound hypoglycemia = low glucose concertation within 6 hr of successful treatment
  - Recurrent hypoglycemia = low glucose after successful treatment, within 48 hr after birth
  - Continuous glucose monitoring sensor (blinded) used in 74% of subjects and this captured about 23% of the episodes of low glucose

Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

The Sugar Babies Study (Dextrose Gel)



Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

Dextrose Gel Decreases NICU Admissions for Hypoglycemia

	Dextrose gel (n=118)	Placebo gel (n=119)	Relative risk or median difference (95% CI)	p value
Volume of study gel (mL/kg)	0·84 (0·43–2·44)	0·97 (0·47–2·49)	0·005 (–0·01 to 0·02)	0·45
Treatment failure	16 (14%)	29 (24%)	0·57 (0·33 to 0·98)	0·04
Admitted to NICU				
Babies (n)	45 (38%)	55 (46%)	0·83 (0·61 to 1·11)	0·24
For hypoglycaemia (n)	16 (14%)	30 (25%)	0·54 (0·31 to 0·93)	0·03

NNT=9

Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

Dextrose Gel Facilitates Breastfeeding

	Dextrose Gel	Placebo
Any Formula Feeding at 2 Weeks of Age		
	4%	13%*

Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

Dextrose Gel Does Not Lead to Rebound or Recurrent Hypoglycemia

	Dextrose gel (n=118)	Placebo gel (n=119)	Rate ratio or median difference	95% CI	p value
Blood glucose					
Rebound episodes					
Episodes per baby	..	..	1·46	0·67 to 3·26	0·33
0	104 (88%)	109 (92%)	..	..	..
1	12 (10%)	9 (7%)	..	..	..
2	2 (2%)	1 (1%)	..	..	..
Recurrent episodes					
Episodes per baby	..	..	0·89	0·55 to 1·44	0·66
0	90 (76%)	91 (76%)	..	..	..
1	23 (20%)	22 (19%)	..	..	..
2	5 (4%)	4 (3%)	..	..	..
≥3	0	2 (2%)	..	..	..
Interstitial glucose					
Babies (n)	25 (21%)	30 (25%)	..	..	..
Rebound episodes					
Episodes per baby	..	..	1·20	0·40 to 3·57	0·73
0	20 (80%)	25 (83%)	..	..	..
1	3 (12%)	3 (10%)	..	..	..
2	2 (2%)	2 (7%)	..	..	..
Recurrent episodes					
Episodes per baby	..	..	0·44	0·21 to 0·86	0·01
0	16 (64%)	18 (60%)	..	..	..
1	8 (32%)	4 (13%)	..	..	..
2	0	3 (10%)	..	..	..
≥3	1 (4%)	5 (17%)	..	..	..

Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

Dextrose Gel Does Not Correct Hypoglycemia More Rapidly Than Feeding Alone

	Dextrose Gel	Placebo
Time taken for interstitial glucose concentration to be restored		
Minutes (Median, 95% CI)	20.3 (0.2-215.4)	22.8 (1.9-165.2)

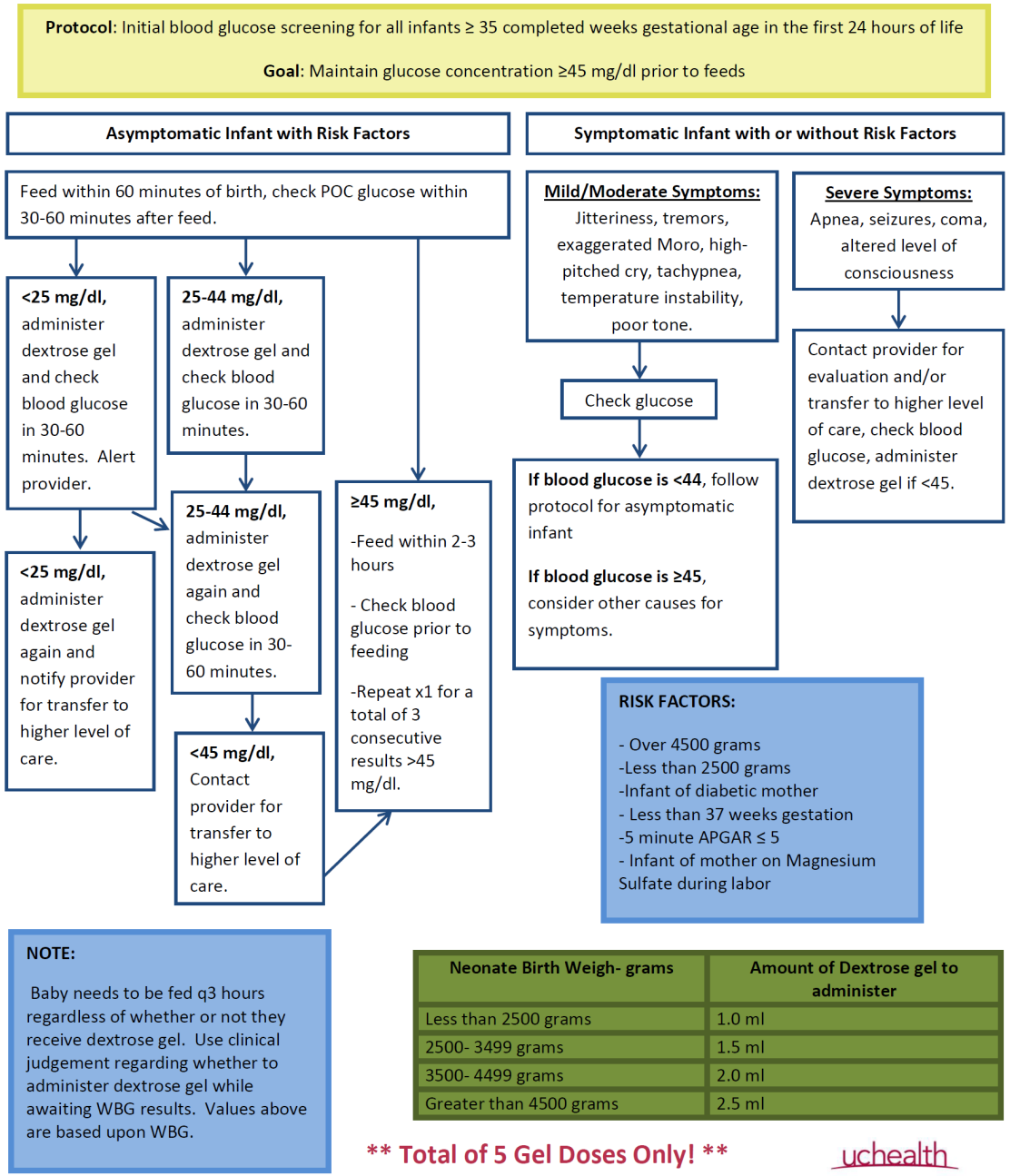
Harris DL, et al. *Lancet*. 2013; 382(9910):2077-2083.

Two Year Outcomes Are Equivalent Between Dextrose Gel and Placebo

	n	Randomized to dextrose gel	n	Randomized to placebo gel	RR or mean difference (95% CI)	*P* value
Age at assessment, mo	90	24.2 ± 1.2	94	24.5 ± 1.9	−0.31 (−0.77 to 0.15)	.18
Primary outcomes						
Neurosensory impairment	90	34 (38%)	94	32 (34%)	1.11 (0.75 to 1.63)	.60
None		56 (62%)		62 (66%)		
Mild		28 (31%)		31 (33%)		
Moderate		5 (6%)		1 (1%)		
Severe		1 (1)		0 (0%)		
Processing difficulty	84	8 (10%)	87	16 (18%)	0.52 (0.23 to 1.15)	.10
Secondary outcomes						
Developmental delay	90	31 (34%)	93	30 (32%)	1.07 (0.71 to 1.61)	.75
None		59 (66%)		63 (68%)		
Mild		25 (28%)		29 (31%)		
Moderate		5 (6%)		1 (1%)		
Severe		1 (1%)		0 (0)		
Cerebral palsy		2 (2%)		0 (0)		
Bayley-III Composite scores						
Cognitive	90	93 ± 11	93	94 ± 9	−1.30 (−4.21 to 1.61)	.38
Language	89	96 ± 14	93	96 ± 13	−0.72 (−3.14 to 4.58)	.71
Motor	90	99 ± 10	93	99 ± 9	−0.36 (−3.04 to 2.33)	.80
Social emotional	88	105 ± 15	90	104 ± 16	−0.43 (−4.12 to 4.99)	.85
General adaptive	89	101 ± 13	91	99 ± 14	1.34 (−2.70 to 5.38)	.52
Executive function	87		92			
Composite score		10.9 ± 4.1		10.0 ± 4.0	0.93 (−0.24 to 2.11)	.12
Children with z score <−1.5		5 (6%)		8 (9%)	0.66 (0.22 to 1.94)	.45
BRIEF-P Index scores	89		93			
Inhibitory self control		55 ± 11		54 ± 10	1.09 (−1.88 to 4.06)	.47
Flexibility		52 ± 10		52 ± 10	0.24 (−2.67 to 3.15)	.87
Emergent Metacognition		60 ± 12		58 ± 12	2.17 (−1.26 to 5.60)	.21
Global Executive Composite		58 ± 11		56 ± 11	1.71 (−1.48 to 4.89)	.29
Vision	86		89			
Motion coherence threshold		40.2 ± 12.8		41.5 ± 15.7	−1.31 (−5.55 to 2.93)	.55
Children with z score >1.5		4 (5%)		8 (9%)	0.52 (0.16 to 1.66)	.27
Vision problem	90	26 (29%)	93	23 (25%)	1.17 (0.72 to 1.89)	.53
Refractive error	51	3 (6%)	49	5 (10%)	0.58 (0.15 to 2.28)	.43

Harris, 2015

University of Colorado Hospital Well Baby Nursery and NICU



Mary Kohn

Jim Barry

Bill Hay

Paul Rozance

Started January 2017

Drastically reduced NICU admissions for “low glucose not responsive to early feeding.”

Dextrose Gel - CAUTION!!

Beware of the:

- Term baby with symptomatic hypoglycemia who has no risk factors
  - Strongly consider investigating these babies for a persistent hypoglycemia disorder
- Mothers with the following characteristics:
  - Young, inexperienced, first time mother
  - Trying to breastfeed for the first time
  - Uncertain in anyway
  - Any sign of illness
  - Difficulties breastfeeding in the nursery
  - Limited home support
  - Keep these women and their infants in the nursery until everything is normal, and stays that way.

Other Strategies to Safely Manage Hypoglycemia Breastfeeding Is Best!

Table II. The impact of treatment choices and infant characteristics on the change in blood glucose concentration (mg/dL)

Factors		Factor present	Factor absent	Univariate analysis		Multivariable analysis	
	n (%)	Change (SE)	Change (SE)	Marginal change (95% CI)	*P* value	Marginal change (95% CI)	*P* value
Age (hours)	295 (100)	—	—	0.05 (–0.5 to 1.5)	.32	—	—
Initial glucose concentration	295 (100)	—	—	–0.1 (–0.3 to 0.1)	.51	–0.1 (–0.3 to 0.1)	.37
Dextrose gel	147 (50)	13.3 (1.0)	10.0 (0.7)	3.3 (0.9 to 5.7)	.007	3.0 (0.7 to 5.3)	.01
Male sex	143 (48)	11.0 (0.9)	12.3 (0.8)	–1.7 (–4.1 to 0.8)	.18	—	—
Milk							
Expressed breast milk	117 (40)	10.3 (0.9)	12.6 (0.8)	–1.9 (–4.3 to 0.4)	.11	–1.4 (–3.7 to 0.9)	0.25
Breast	168 (57)	12.5 (0.7)	10.5 (1.0)	1.7 (–0.6 to 4.0)	.15	2.0 (–0.3 to 4.2)	.09
Formula	55 (19)	15.5 (1.8)	10.8 (0.6)	4.2 (1.3 to 7.2)	.004	3.8 (0.8 to 6.7)	.01

However, breastfeeding was associated with a reduced odds of a second treatment of hypoglycemia!
(OR 0.52, 95% CI 0.28-0.944; *P*<0.05)

Harris DL, et al. *J Pediatr*. 2017; 190:136-141.

Other Strategies to Safely Manage Hypoglycemia–
Are All Risk Factors the Same?

- Normal Glucose Utilization Rate is 4-6 mg/kg/min
- IDM/LGA → **GIR = 3-5 mg/kg/min**
  - Increased adiposity
    - Less glucose utilization per kg
  - Hyper-responsive insulin secretion
- IUGR/SGA → **GIR = 6-8 mg/kg/min**
  - Decreased adiposity
  - Increased brain to body weight ratio
    - More glucose utilization per kg
  - Hyper- or Hypo responsive insulin secretion
- Late Preterm or Otherwise NPO → **GIR = 4-7 mg/kg/min**

Rozance PJ, Hay WW. *Matern Health, Neonatol, and Perinatol*. 2016; 2:3..

Other Strategies to Safely Manage Hypoglycemia On The Horizon:

- Accurate devices to measure glucose concentrations
  - Typical bedside glucometers are less accurate than blood gas biosensors.
    - 2017 British Association of Perinatal Medicine:

      "The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability."
  - Role of newer generation bedside glucometers.
  - Continuous interstitial glucose monitoring sensors
- Rapid and accurate measurement of alternative fuels
- Non-glucose based methods to screen for persistent severe hypoglycemia disorders
- Clinical and translational research to better stratify patients based on risk for prolonged hypoglycemia and to better screen for persistent hypoglycemia disorders

Low Glucose Concentrations Are Common in the First 48 Hours of Life

The Journal of Pediatrics

514 (100%)

254 (49%) Normal Glucose

260 (51%) Low Glucose

Incidence of Neonatal Hypoglycemia in Babies Identified as at Risk

Deborah L. Harris, MHSc (Hons)[1,2], Philip J. Weston, MBChB[1], and Jane E. Harding, MBChB[2]

- At risk groups - SGA, IDM, LGA, Late Preterm
- Plasma glucose measured before each feed for 48 hours
- Hypoglycemia defined as a plasma glucose ≤ 47 mg/dL

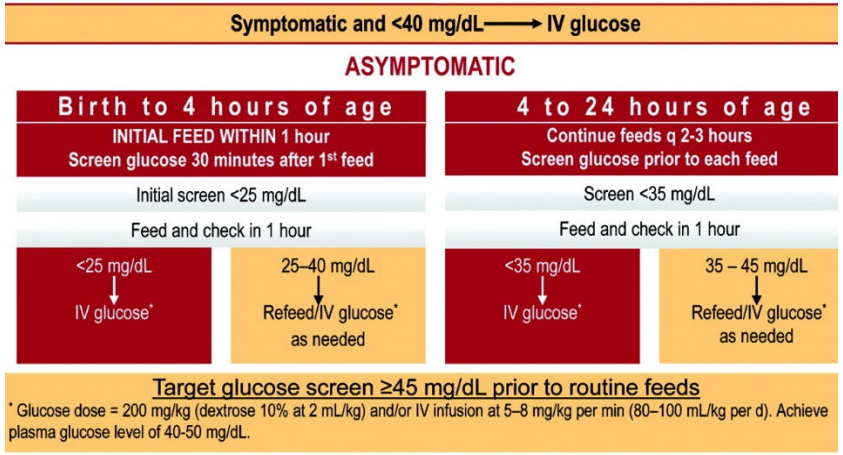
- 50% had a low glucose concentration
  - More common if using continuous interstitial glucose monitoring

- These at risk groups represent over 25% of all newborns
- At least 12.5% of all newborns have a low glucose concentration
  - >500,000/year in the United States
- 10% of these needed intravenous dextrose
  - >50,000/year in the United States

Harris, 2010, 2012, 2013

What Targets to Use for Treatment?

AAP



Target glucoses >40-50 mg/dL in the first 24 hours

PES

Target >50 mg/dL in the first 48 hours

Target >60 mg/dL if on IV Dextrose or age >48 hours

Who to Investigate for a Hypoglycemic Disorder?

AAP	PES
If it is not possible to maintain blood glucose concentrations of greater than 45 mg/dL after 24 hours of using 5-8 mg/kg/min of glucose infusion	Neonates with severe hypoglcyemia • Symptomatic hypoglycemia, especially neurologic symptoms, in an otherwise healthy infant • Required prolonged and/or high rates of dextrose infusion to treat hypoglycemia Neonates unable to consistently maintain pre-prandial glucose concentrations >60 mg/dL after 48 hours of age Family history of a genetic hypoglycemia disorder Abnormal physical exam features suggestive of a syndromic hypoglycemia disorder (midline facial malformation, microphallus, Beckwith-Wiedemann)

How to Investigate for a Hypoglycemic Disorder?

AAP	PES
Insulin should be measured when the glucose is <40 mg/dL An endocrinologist should be consulted	While glucose is <50mg/dL* • Insulin • Beta-hydroxybutyrate • Cortisol • Growth hormone • Lactate • ± Subcutaneous glucagon – Be prepared to treat rebound hypoglycemia * assumes an accurate device

When to Obtain Critical Labs?

PES

While glucose is <50 mg/dL (* caveat for bedside glucometers)

- At presentation if >48 hours of age
  - Extremely difficult in the first 4 days of life
- While weaning IV dextrose
- Pre-feed
- Provoked by a fast

Done before treatment

Is the Patient Ready for Discharge?

AAP	PES
Be certain that the infant can maintain normal plasma glucose concentrations on a routine diet for a reasonably extended period before discharge • through at least 3 feed-fast periods	Maintain glucose concentrations through regular feed-fast cycles: • >50 mg/dL if <48 hours of age • >60 mg/dL if >48 hours of age "Safety" fasting challenge • 6-8 hour fast (one skipped feed) – Maintain glucose >60 mg/dL, for most patients – Special considerations for patients with a known risk of a genetic hypoglycemia disorder

"Discharge from the nursery should not occur until these infants maintain glucose levels >70 mg/dL through several normal fast-feed cycles."

Adamkin DH, *J Perinatol*. 2016