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Neonatal Hypoglycemia—Facts, Fiction, and State of the Art and Science

William W. Hay, Jr. MD

Director, Child and Maternal Health Program,
Director, Perinatal Clinical-Translational Research Center,
Colorado Clinical and Translational Sciences Institute

Scientific Director: Perinatal Research Center

University of Colorado School of Medicine

bill.hay@ucdenver.edu

What is Neonatal Hypoglycemia?

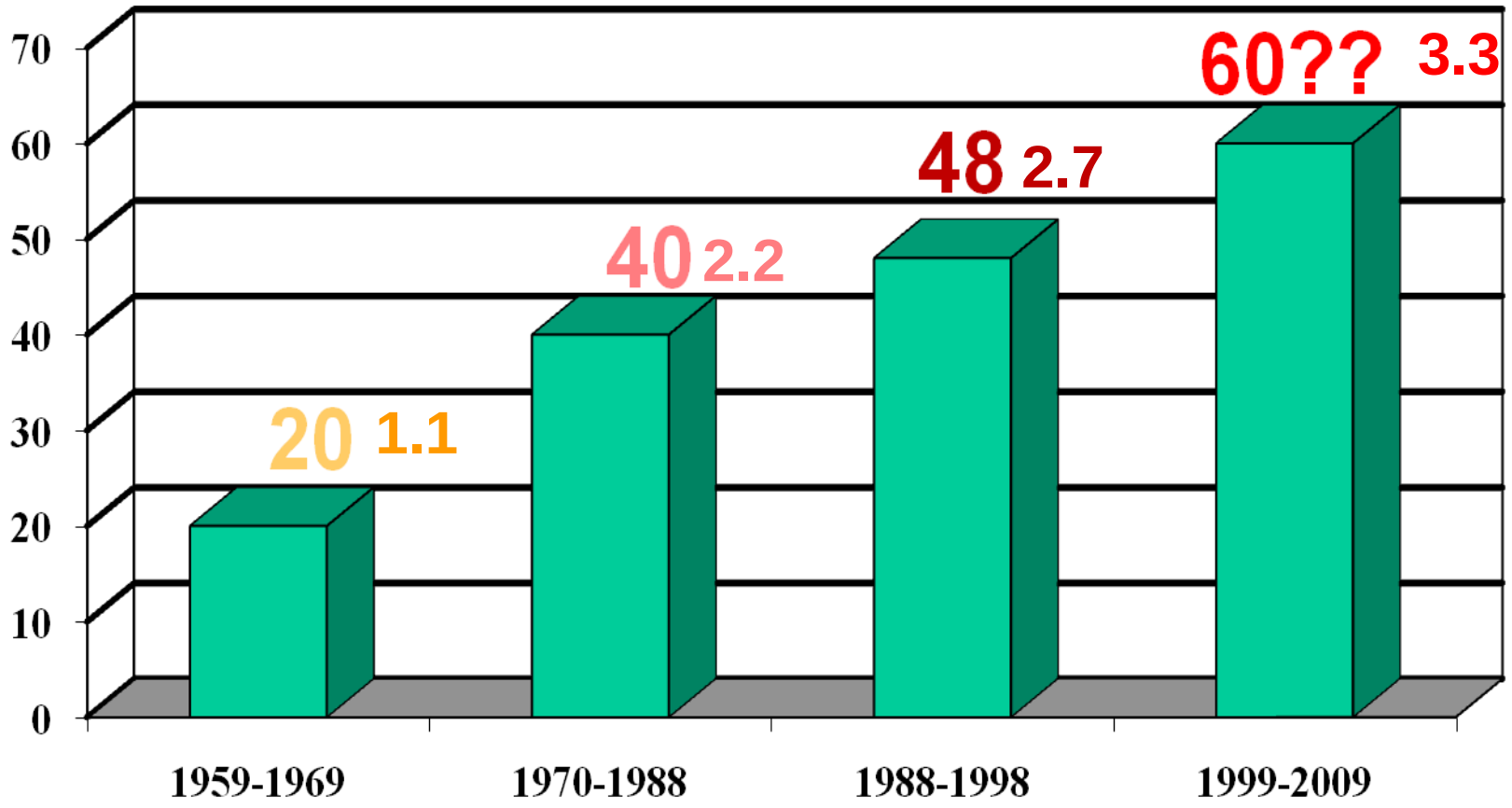
In 1937, Hartmann and Jaudon reported 9 neonates out of 285 infants and children with varying degrees of severity of hypoglycemia defined as:

1) "Mild" 40-50 mg/dl "true sugar" values (2.2-2.8 mmol/L)

2) "Moderate" 20-40 mg/dl "true sugar" values (1.1-2.2 mmol/L)

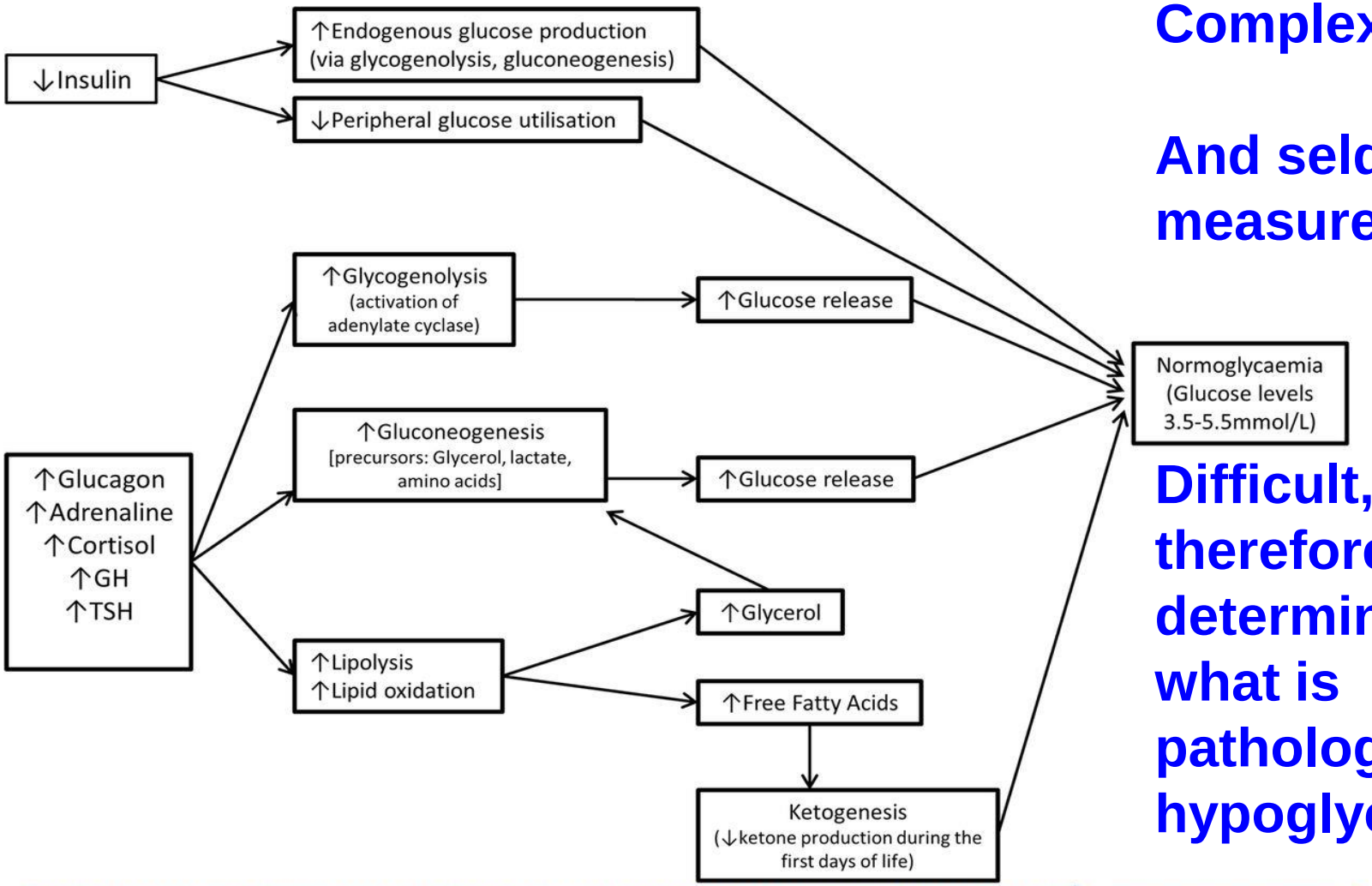
3) "Extreme" <20 mg/dl "true sugar" values (<1.1 mmol/L)

Nothing has changed **except arbitrarily increasing the lower limit of "normal" glucose concentrations, which has been done without research and with no evidence that outcomes have been improved, or even affected!**



Cornblath, Hot Topics, 2000

Metabolic, endocrine, and physiological changes that occur after birth to allow normal neonatal adaptation to extra-uterine life--



Complex--!!

And seldom measured.

Difficult, therefore, to determine what is pathological hypoglycemia.

Maria Güemes et al. Arch Dis Child 2016;101:569-574

Perhaps a better starting point: Definition of Normoglycemia

- Most definitions, none evidence-based, are above ~2.5 mmol/L (> ~45mg/dL).
- But >1.7 mM (>30 mg/dl), or ~5th percentile, for Breast Fed, Healthy, AGA Term newborns.
- None defines the glucose concentration below which irreversible neurological injury invariably or even probably occurs.

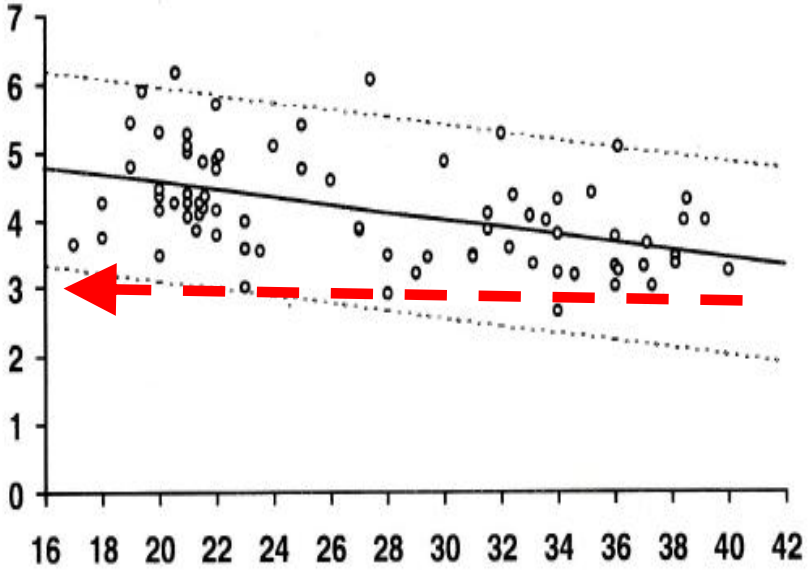
Hay , Rozance. Biol Neonate 2006

Starting Point: Definition of Normoglycemia

The normal human fetus and the normal human term neonate have the same statistical lower limit glucose concentration, ~3.0 mmol/L.

Normal Fetus

>3.0 mM (54 mg/dL)



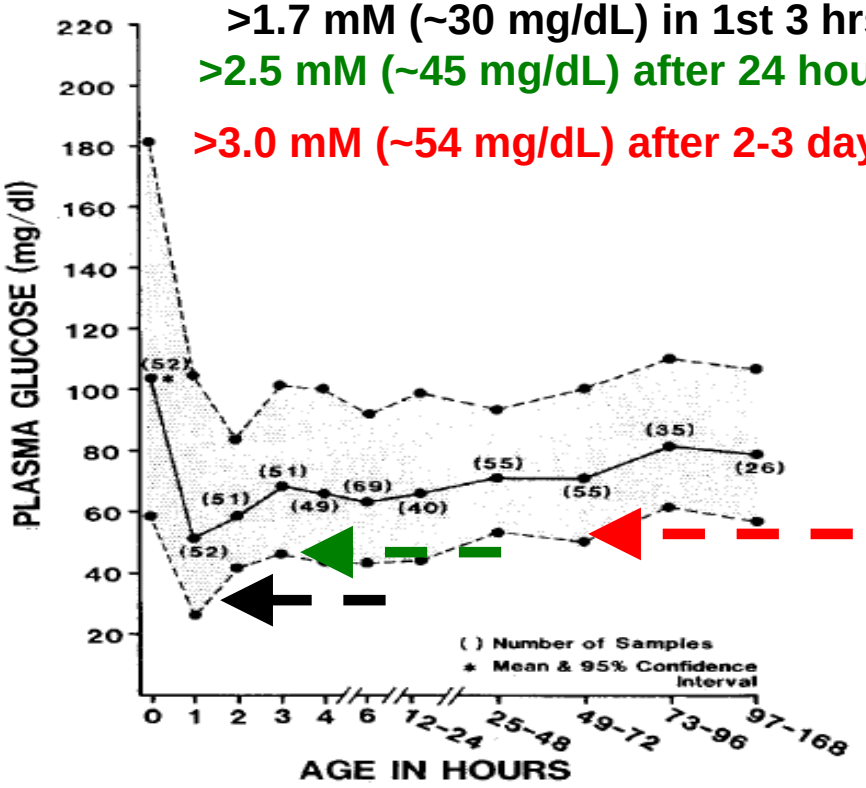
Marconi AM, et al., 1996

Normal Neonate

>1.7 mM (~30 mg/dL) in 1st 3 hrs,

>2.5 mM (~45 mg/dL) after 24 hours,

>3.0 mM (~54 mg/dL) after 2-3 days.



Srinivasan G, et al., 1986.

But—this lower limit "normal" glucose concentration does not determine neurological injury at lower levels.

And, there is large variation among "normals".

Plasma Glucose values in Normal Healthy Term, AGA, Breast-fed infants: mean ~10 mg/dL less than in formula fed term AGA infants; plus a very wide range.

Age (hours)	Mean mg/dl	Median mg/dl	Range mg/dl	Interquartile Range
3	54	50	25 - 149	41.4-59.4
6	54	50	29 - 97	43.2-59.4
24	52	52	18 - 137	46.8-59.4
72	54	50	25 - 166	46.8-59.4

18 = 1 mM
25 = 1.4 mM
47 = 2.6 mM

Wight, et al., Breastfeeding Medicine 2006

Although plasma glucose concentrations measured serially in AGA/SGA and exclusively breastfed infants tend to stay the same over the first 3 days of age.

Diwakar KK, **Sasidhar** MV. Arch Dis Child Fetal Neonatal Ed 2002;87:F46-8

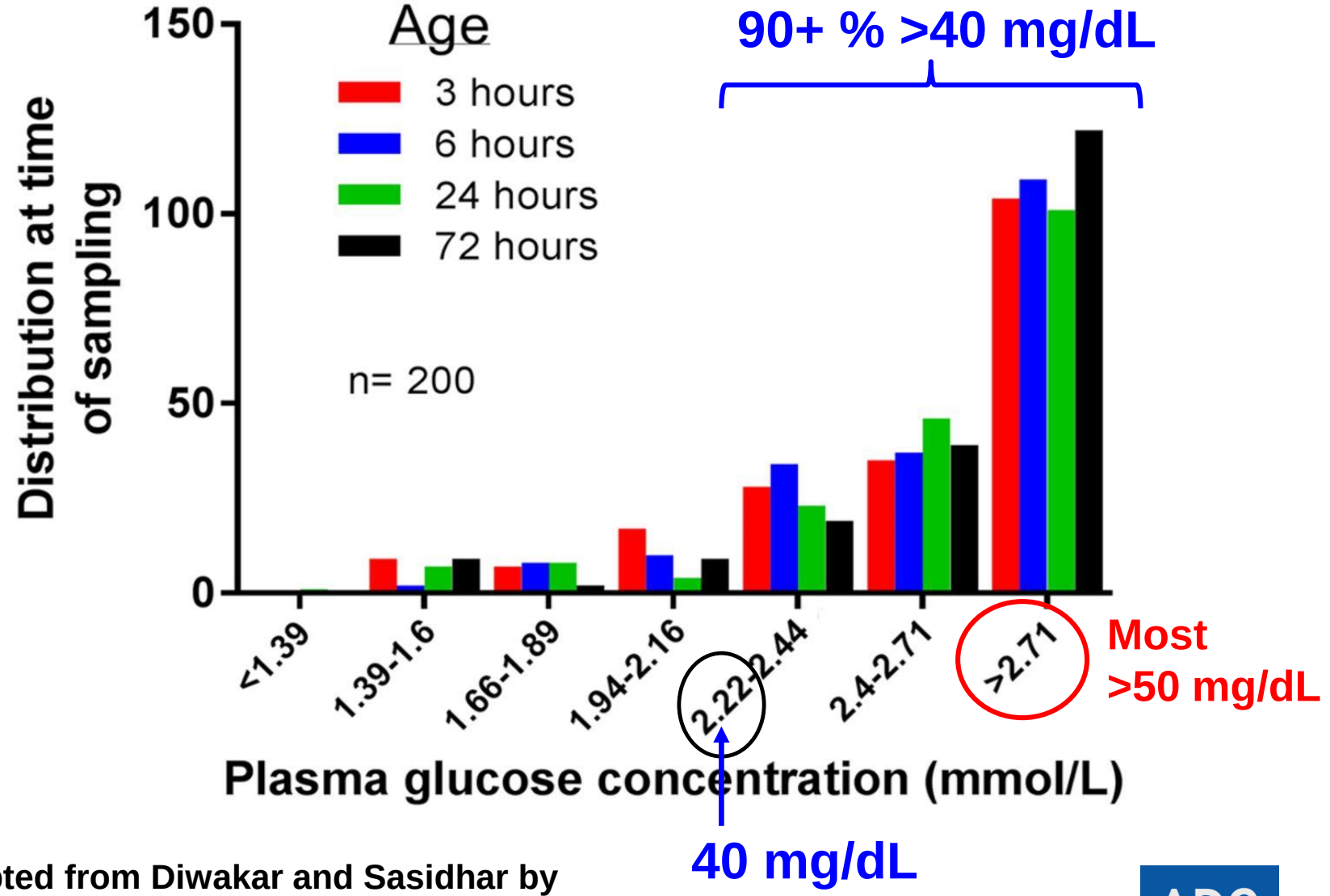


Figure adapted from Diwakar and Sasidhar by Maria Güemes et al. Arch Dis Child 2016;101:569-574.

ADC

Nevertheless, the incidence of neonatal "hypoglycemia" **(≤ 47 mg/dl; 2.6 mM)** in **"at risk"** infants in 1st 48 hours of life is quite high.

Harris DL, et al. J Pediatr 2012;161:787-791.

514 Infants (100%)

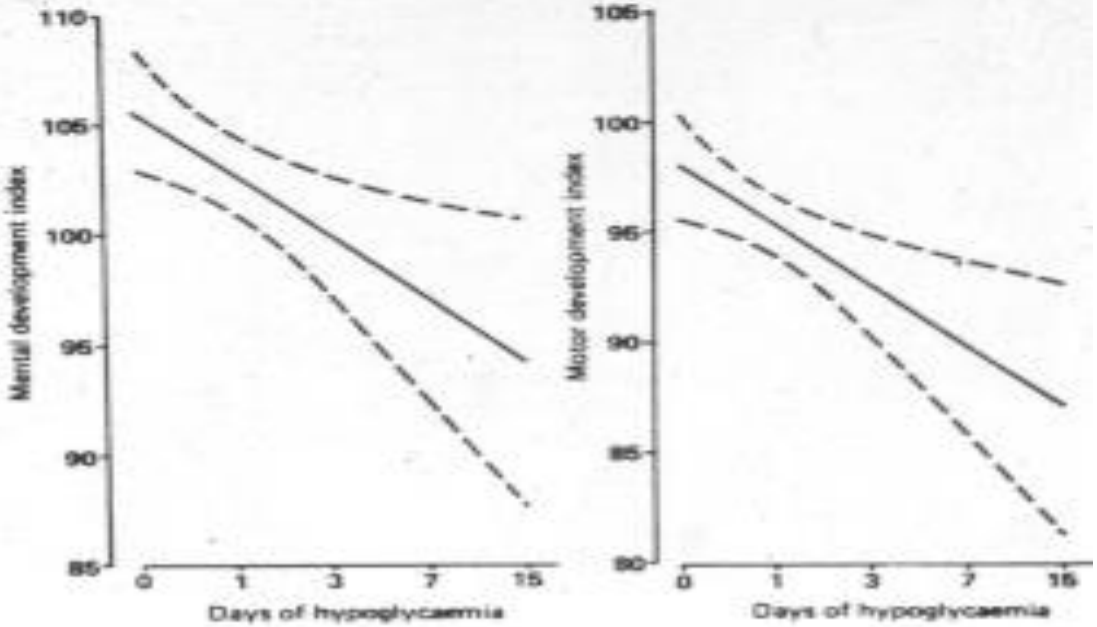
254 (49%) **Normal Glucose**

260 (51%) **Low Glucose**

- **At risk groups - SGA, IDM, LGA, Late Preterm** (<2500,>4500g)
- Plasma glucose measured before feeds q 3-8 first 48 hours (d/c levels after 3 consecutive normals)
- 51% low glucose concentration, **19% > 1 episode**
- **These "at risk" groups represent over 25% of all newborns**
- At least 12.5% of all newborns have a low glucose concentration, >550,000/year in the United States

What happens to them?

Long term Effects of Repeated, Asymptomatic, Low Glucose Concentrations?



Logarithm of days of recorded hypoglycaemia <2·6 mmol/l related to Bayley mental development index and Bayley psychomotor development index at 18 months (corrected age). Regression slopes and 95% confidence intervals (broken lines) are shown adjusted for days of ventilation, sex, social class, birth weight, and fetal growth retardation. Data shown are for both sexes and all social classes combined and for no ventilation. For infants ventilated for 1-6, 7-14, or >14 days subtract 5, 10, or 15 points respectively for mental development index and 4·5, 9·0, or 13·5 points for psychomotor development index.

Lucas, et al
BMJ VOLUME 297 19 NOVEMBER 1988

Repeated glucose concentrations below 47 mg/dL or ~2.6 mM in preterm infants associated with worse developmental outcome (at least to 18 months of age).
Lucas, et al. 1988

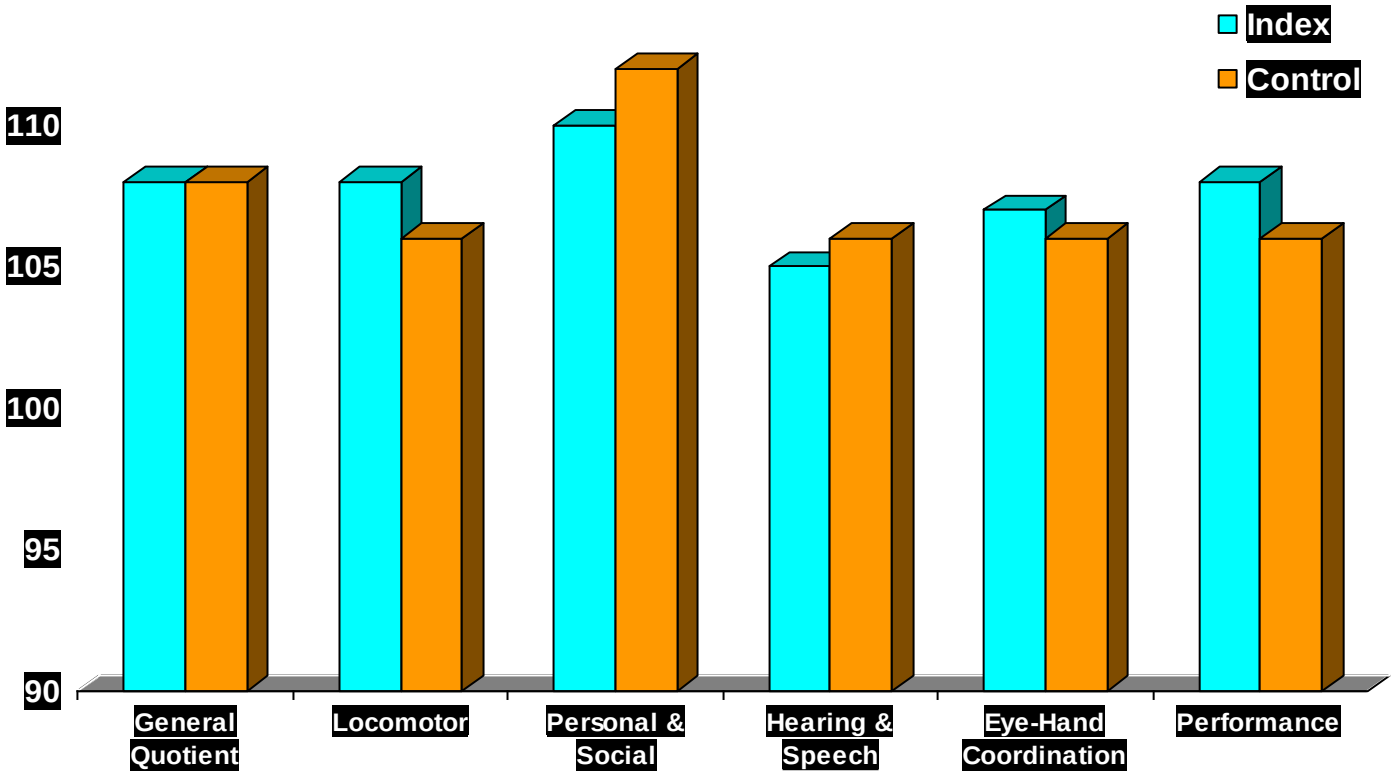
Not sustained at 7-8 years of age! Later, author said method was not optimal.

Cohort of asymptomatic "hypoglycemic" preterm infants followed for 15 years.

Ford, Kelly, *Tin*: Northern UK Nursing Initiative Trial.

Tin W et al. Pediatrics 2012;130:e1497-e1503

MEAN GRIFFITHS DEVELOPMENTAL QUOTIENTS OF 47 MATCHED PAIRS



Conclusion: This prospective study found *no evidence* to support the contention that *asymptomatic low blood glucose levels* are damaging in the preterm baby in the first 10 days of life.

P-values for 'Transient Hypoglycemia' as a Predictor of Early School Test Proficiency Using Different Cutoffs

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

Why just these?

30 = 1.7 mM, 35 = 1.9 mM, 40 = 2.2 mM, 45 = 2.5 mM, 50 = 2.8 mM

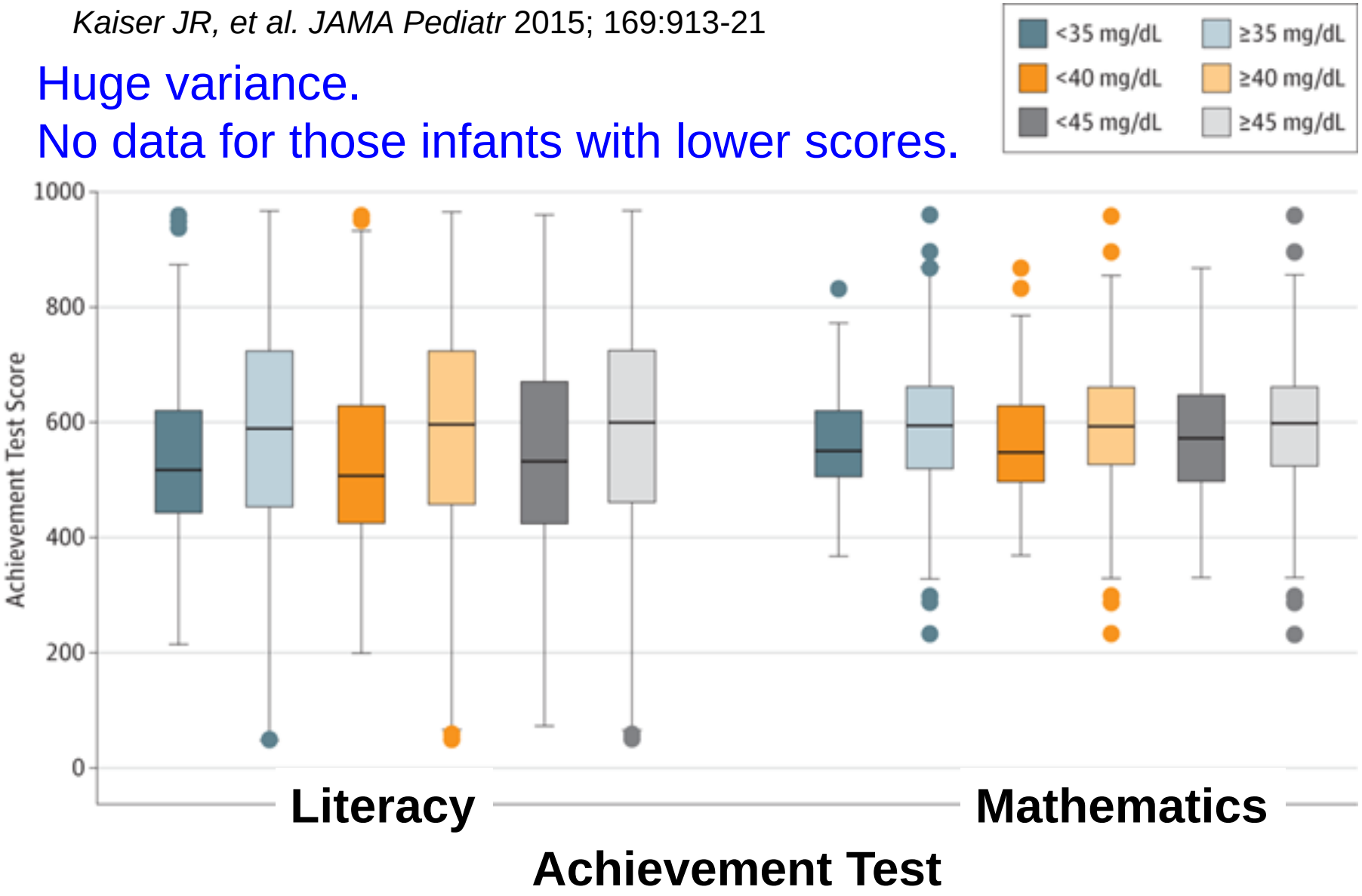
Kaiser JR, et al. JAMA Pediatr 2015; 169:913-21

4th Grade Literacy and Mathematics Achievement Test Scores are Lower (????) for Hypoglycemic Term Newborns

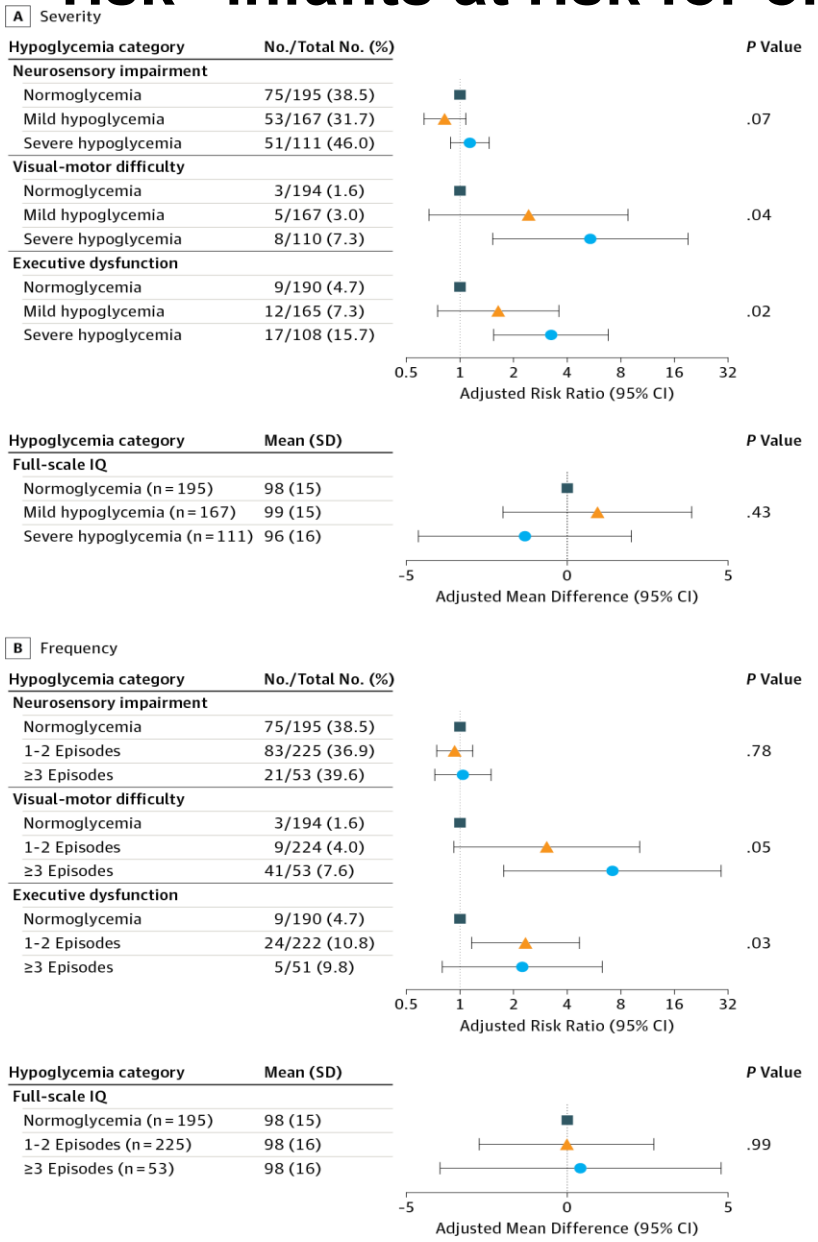
Kaiser JR, et al. JAMA Pediatr 2015; 169:913-21

Huge variance.

No data for those infants with lower scores.



Only severely hypoglycemic (<36 mg/dL, 3 mmol/L) “high risk” infants at risk for only selective adverse outcomes.



614 neonates >32 weeks' gestation with at least 1 risk factor for hypoglycemia (IDM, Preterm, LGA, SGA, acute illness). Glucose measured up to 7 days after birth.

Infants with hypoglycemia (<47 mg/dL) treated to keep glucose ≥47 mg/dL.

Neurosensory Impairment: NS

Visual Motor difficulty worse with severe hypoglycemia (<36 mg/dL) and more than 1 episode

Executive function worse with severe hypoglycemia (<36 mg/dL) and more than 1 episode

Full Scale IQ: NS

McKinlay CJD, et al. JAMA Pediatr 2017, Aug 7.

Why should we define Neonatal Hypoglycemia?

1. Almost all clinical signs caused by low glucose concentrations improve with glucose treatment.

2. Organic, genetic causes of hypoglycemia that lead to brain injury have glucose values below 20-25 mg/dL (1.1-1.4 mM), intermittently but for prolonged periods, so it makes sense to keep glucose concentrations well above this level.

Hyperinsulinism—excessive glucose utilization

Metabolic blocks (**F**atty **A**cid **O**xidation disorders)

—excessive glucose utilization

Hypopituitarism—inadequate glucose production

And, there is observational “evidence”
(not from controlled, prospective investigations)
of “apparent neurological injury” from severe
hypoglycemia in human neonates ---

Symptomatic hypoglycemic infants, primarily those with severe, protracted, and recurrent neurological conditions such as seizures and coma, plus plasma glucose concentrations of zero to 1.1 -1.4 mM (20-25 mg/dL) for several hours or more, have a poorer prognosis, with abnormalities ranging from learning disabilities to cerebral palsy and persistent or recurrent seizure disorders, as well as mental retardation of varying degrees.

Rozance and Hay, Biol Neonate 2006; 90: 74-86

Why should we not define Neonatal Hypoglycemia?

There has been no prospective controlled trial to assess risks of any one glucose concentration, or range of glucose concentrations, or their duration, or whether treated or untreated, or in relation to other concurrent pathology, in any population of newborn infants, whether normal, sick, full term, preterm, growth restricted, etc.

It is unlikely that such trials ever will be done!

And another problem--

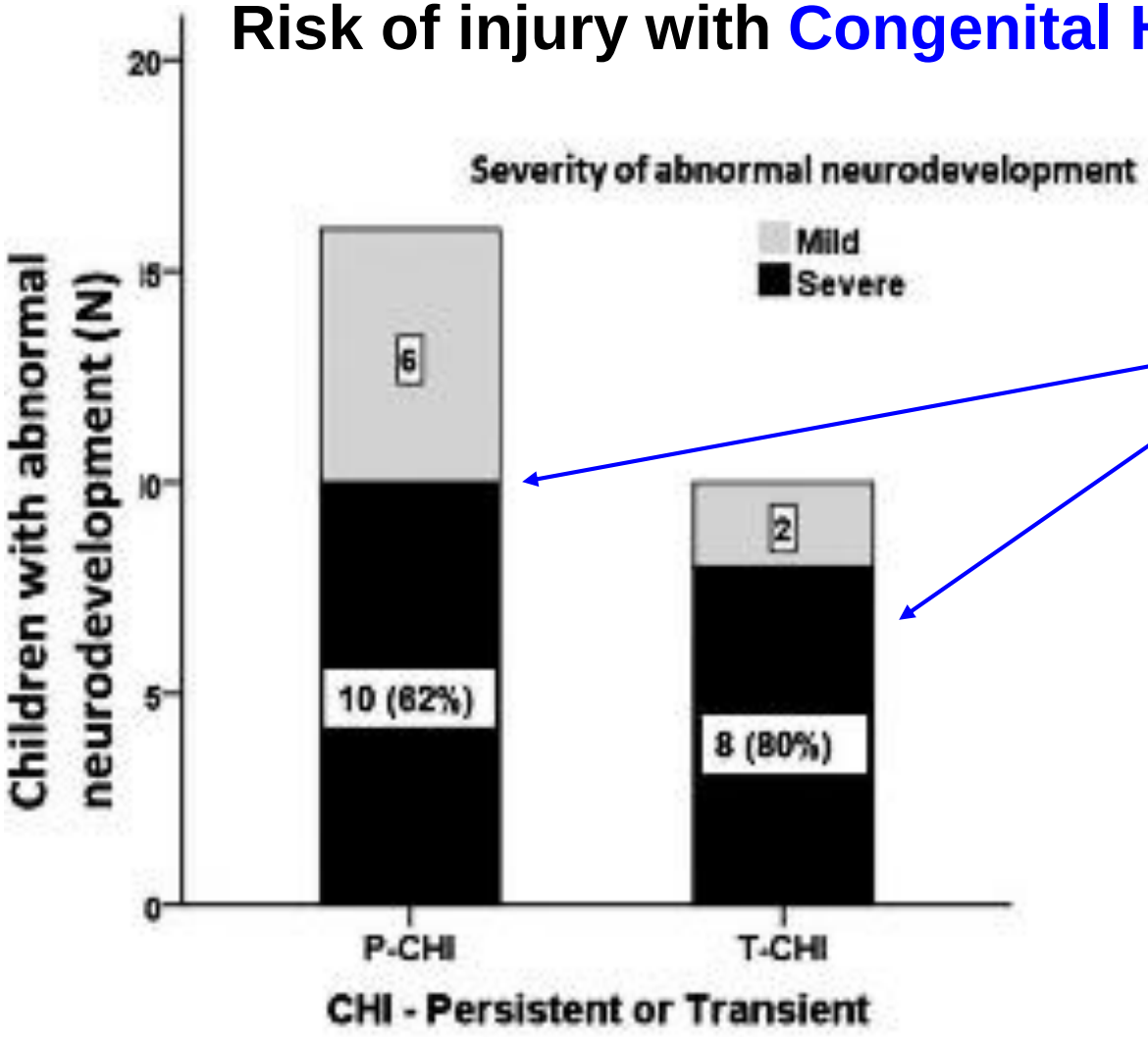
The higher the threshold (> 2.6 mM) and the more often the screens (especially <48 h), the more often asymptomatic infants with low glucose values will be identified, who likely will be over-diagnosed as “hypoglycemic” and potentially over-treated, with no benefit and considerable risk for other adverse outcomes (e.g., NICU admission, IVs, failed breast feeding).

Rozance P, Hay WW, J Pediatrics, 2012

Persistent or Recurrent **Hypoglycemia.**

- These disorders can be severe, and most result in neurological injury. Neonates with repeated, marked, and prolonged, not just brief, transient, hypoglycemia should not go home without a diagnosis.
- Treat with IV glucose until stable! Monitor frequently. Take signs of illness and/or hypoglycemia seriously.
- Maintain glucose concentration constant! (many of these infants have dangerous hyperinsulin conditions).
- Obtain plasma insulin concentrations when glucose concentrations are low—repeat, if possible.
- Establish full enteral feeding before discharge.
- Do not discharge any infant with recurrent, low glucose concentrations until you have proven for 1-2 days that they can maintain normal glucose concentrations before feeding for up to 4-6 hours between feedings.

Risk of injury with Congenital Hyperinsulinism (CHI)



Mild and severe abnormal neurodevelopment for **persistent** (P-CHI) and **transient** CHI (T-CHI); the prevalence of severe abnormal neurodevelopment is similar in both groups, implying that **early severity**, and **duration of hypoglycemia**, are **both important in determining the outcome** of hypoglycemia in children with CHI.

Avatapalle HB et al.
Front Endocrinol
(Lausanne) 2013; 4: 60.

Initial Hypoglycemia and Neonatal Brain Injury in Term Infants with Severe Fetal Acidemia and evidence of Hypoxia/Ischemia.

- Retrospective Chart review 185 Term infants with pH <7.00, 41% Neurologically abnormal
- Odds Ratio 6.3 for severe neurological damage comparing hypoglycemic infants with euglycemc infants
- "Initial hypoglycemia is an important risk factor for perinatal brain injury, particularly in depressed term infants who require resuscitation and have severe fetal acidemia."
- **"It remains unclear, however, whether earlier detection of hypoglycemia, such as in the delivery room, in this population could modify subsequent neurological outcome."**

Salhab, et al, Pediatrics 224:361 (2004)

Glucose Management after Hypoxia-Ischemia

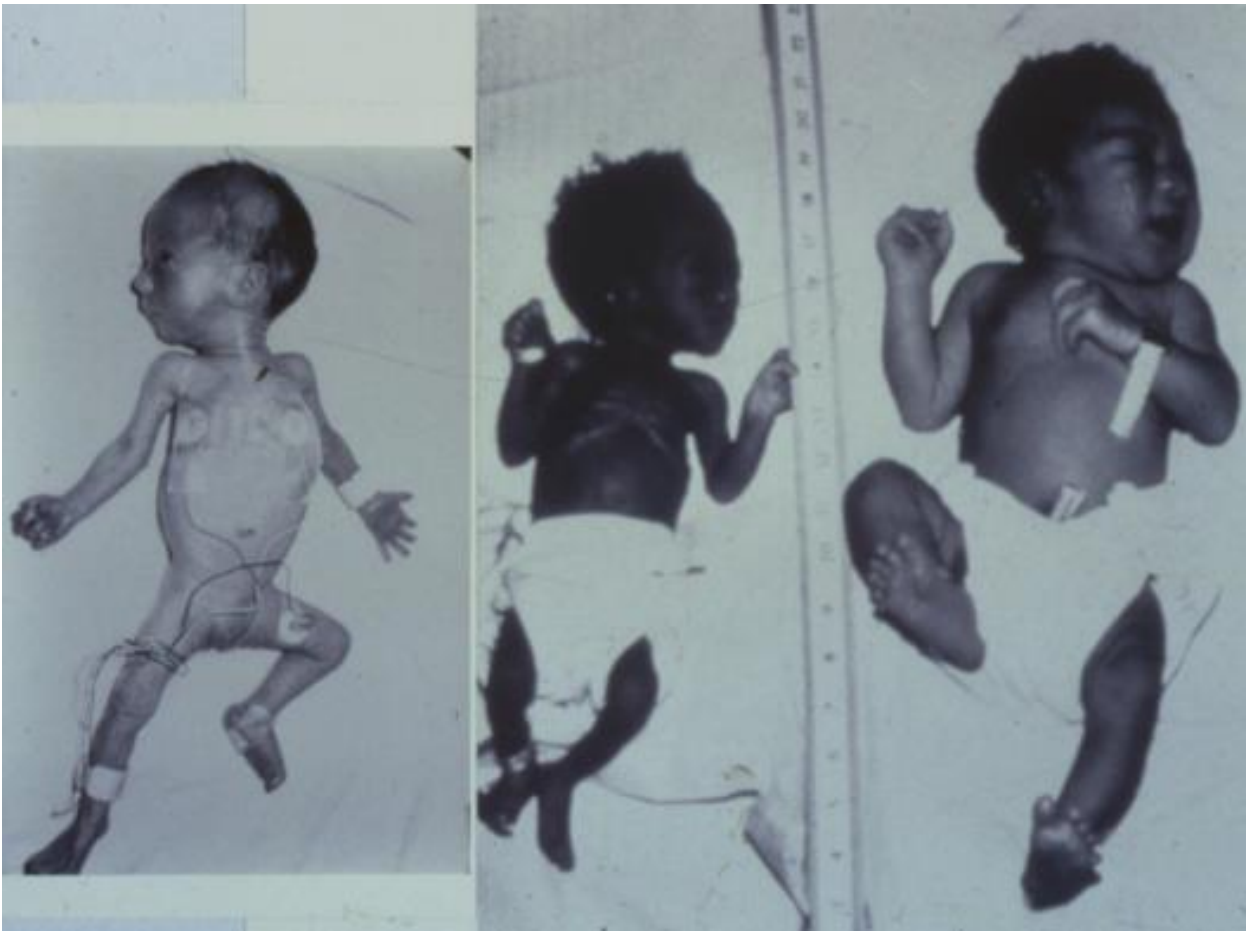
- Measure glucose concentration as soon as reasonable (1st 20-30 minutes in NICU is a "reasonable" guide)
- Measure glucose concentration frequently (every 30 minutes)
- Start IV dextrose infusion as soon as reasonable (1st 30-60 minutes in NICU)
- Adjust glucose infusion rate as needed to maintain **normal** glucose concentrations: **>3 mmol/L, <6 mmol/L** (too high, too low---both are bad)

Persistent Hypoglycemia in IUGR infants.

An increasingly recognized and frustratingly difficult problem to diagnose and treat.

What are the causes?

Asymmetric IUGR fetuses have a greater brain to body/liver ratio, thus greater weight-specific glucose utilization rates.



26 weeks
750 g

40 weeks
1500 g

40 weeks
3200 g

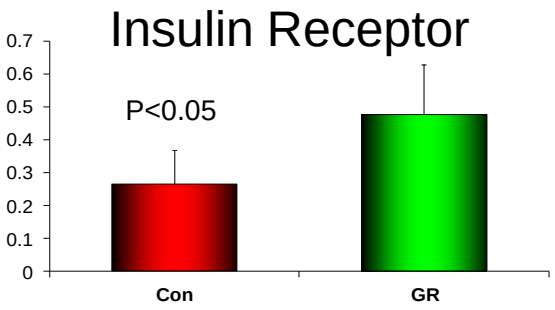
Fetal Glucose Utilization Rates (Sheep)

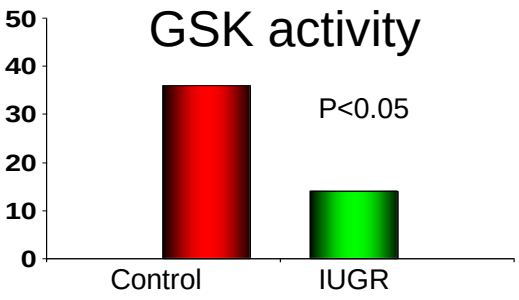
75 Days (50% Gestation)
9.4 mg/kg/min

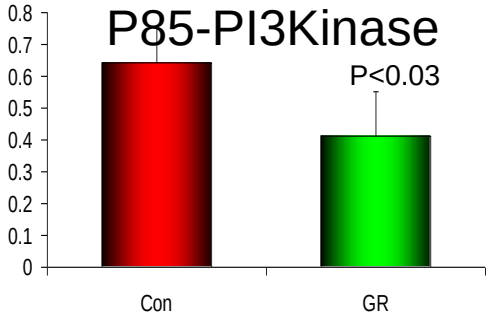
140 Days (93% Gestation)
4.9 mg/kg/min —
”diluted” by organs that don’t use as much glucose as the brain: bone, fat, muscle.

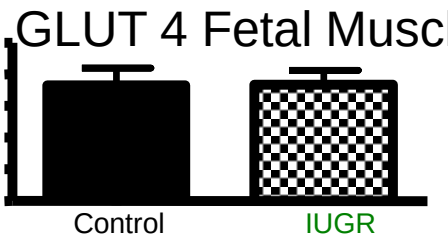
IUGR fetuses more like 75 days, larger relative brain size, without as much bone or fat or muscle.

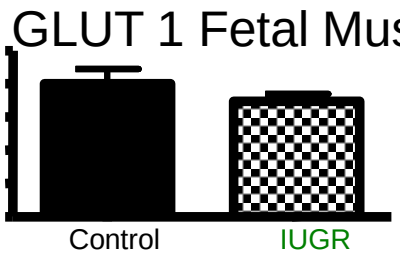
Up-regulated Glucose and Insulin Sensitivity in the IUGR Sheep Fetus.

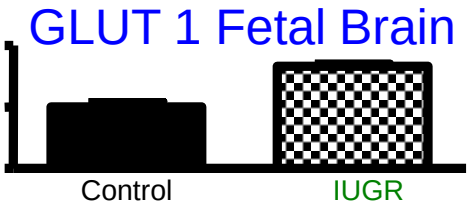






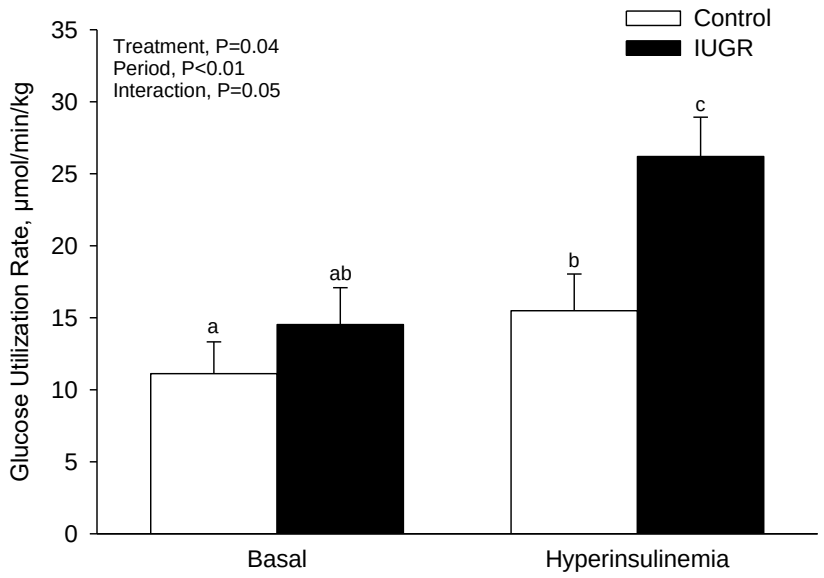


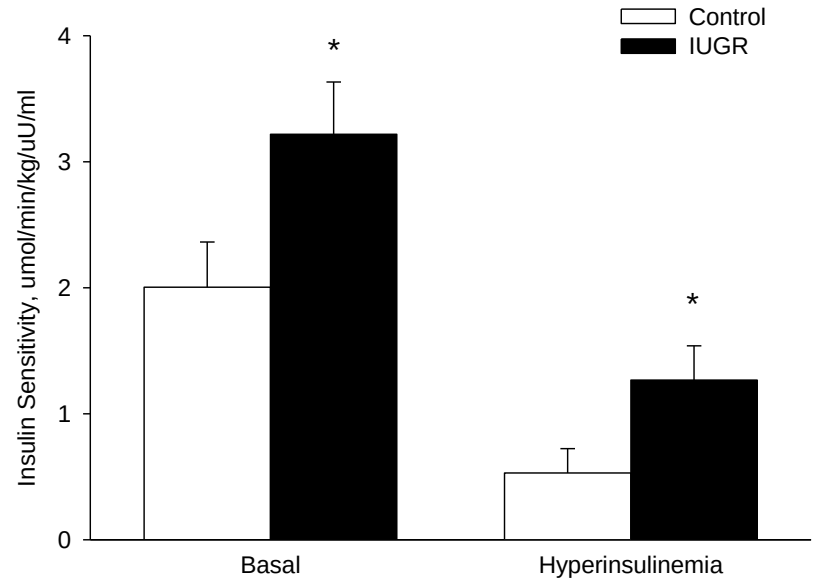




These changes maintain glucose utilization and insulin sensitivity--- i.e. GUR/kg is normal at less than normal [Glu] and [Ins].

	Control	IUGR
GUR	5 mg/kg/min	5 mg/kg/min
[G]	20 mg/dL	10 mg/dL
[I]	12 μU/mL	5 μU/mL





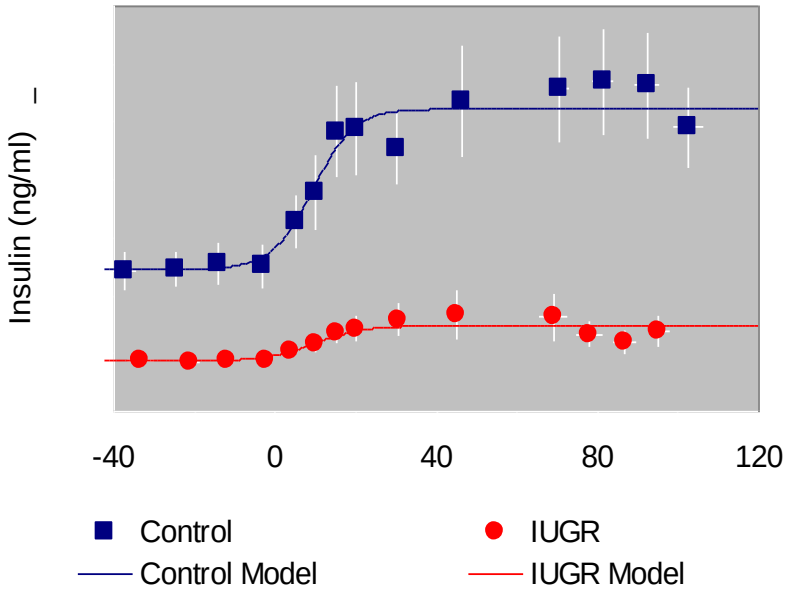
And this up-regulated glucose and insulin sensitivity can persist well into the neonatal and infancy period.

Increased hindlimb glucose utilization rate (GUR) persists in 4-week old IUGR lambs vs. controls,

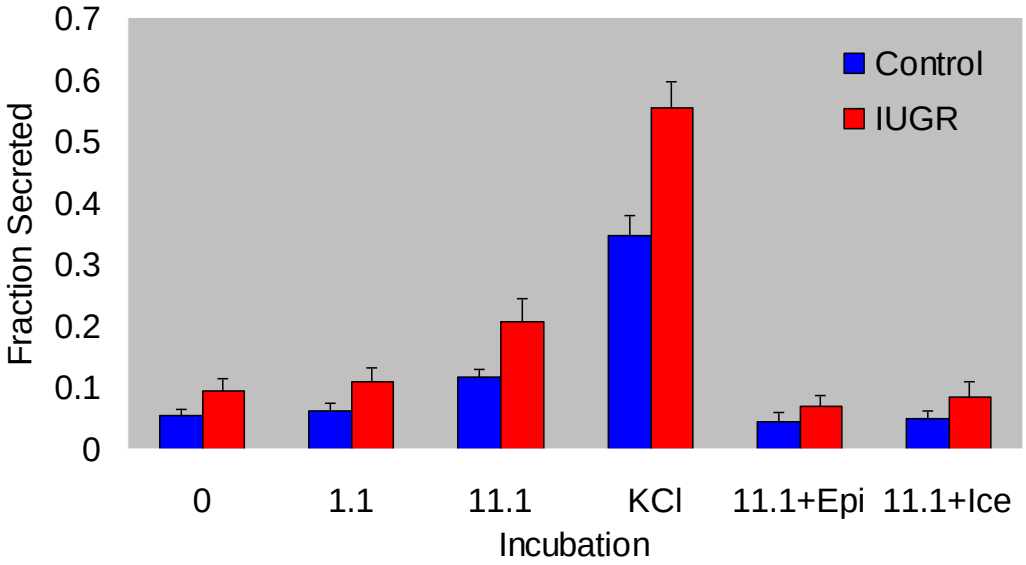
as does hindlimb insulin sensitivity (GUR / [insulin])

Camacho, Frank, Hay, Limesand. Unpublished data.

Although glucose stimulated insulin secretion is reduced in IUGR fetuses---



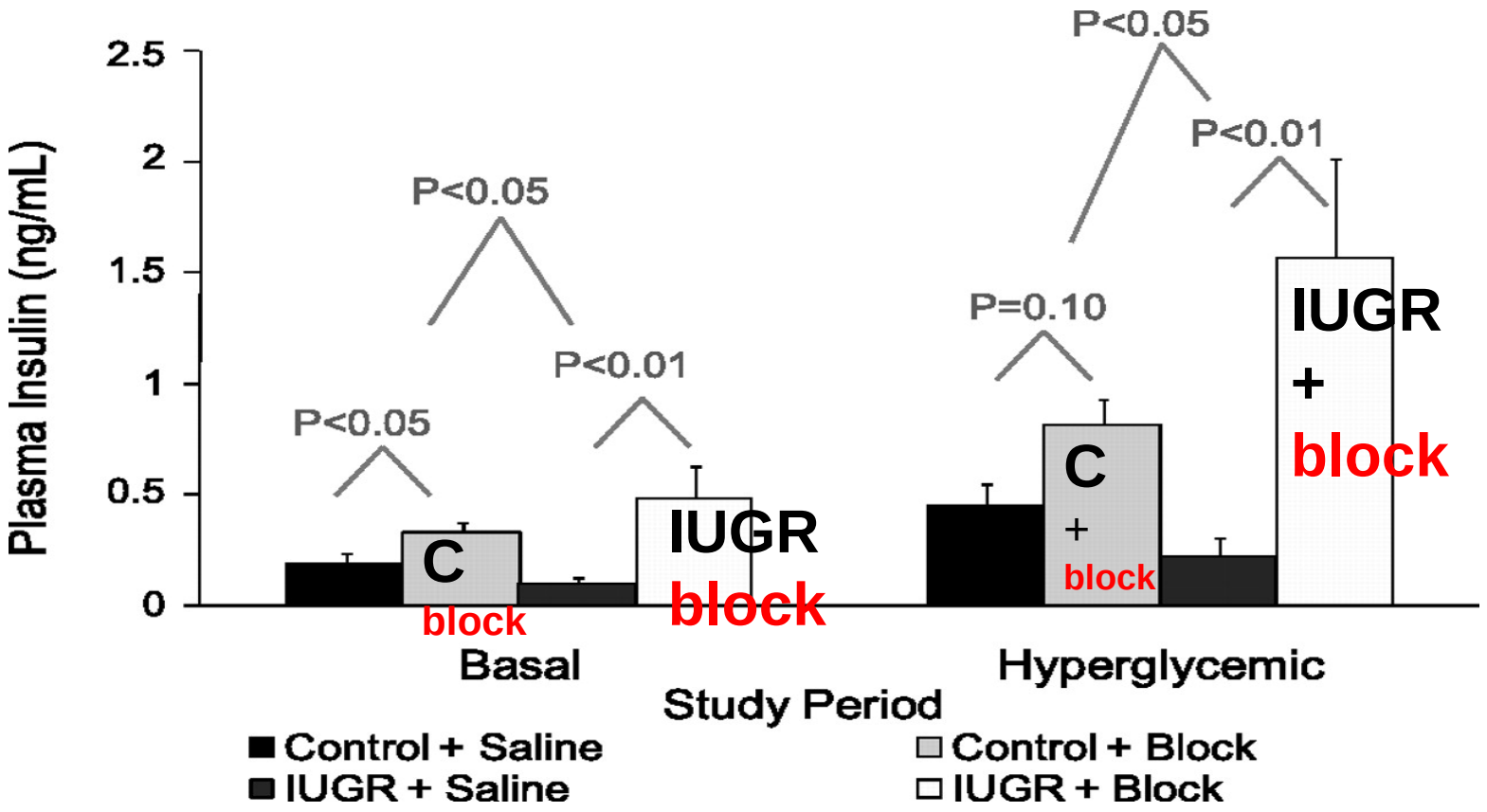
They also have Increased Fractional Islet Insulin Secretion!



Limesand et al. 2006

IUGR—Hypoxia—increased catecholamines.

Fetal insulin concentrations increase with blocking of catecholamines, proof that they suppress insulin secretion.



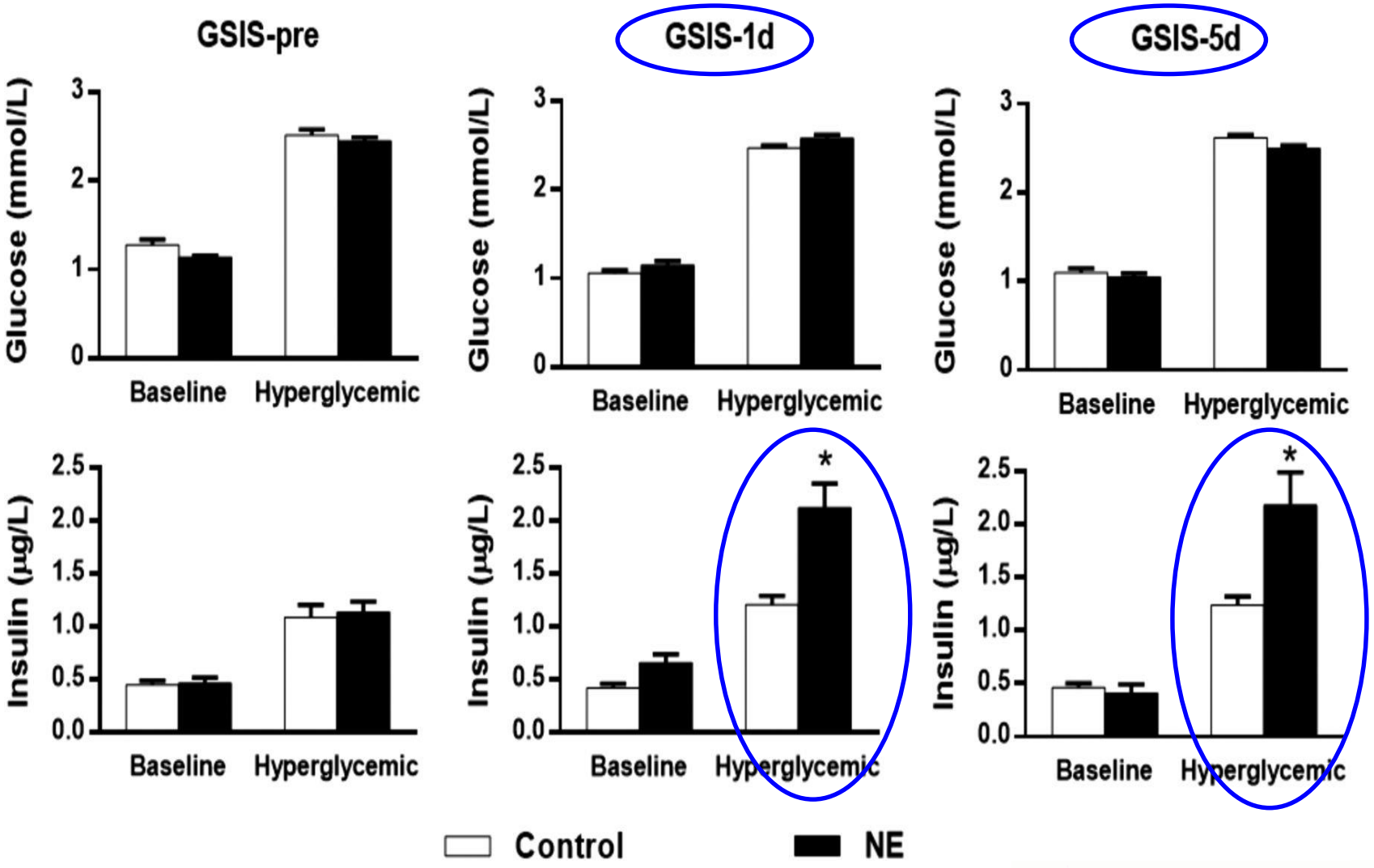
Sean Limesand's studies

Leos R A et al. Am J Physiol Endocrinol Metab 2010;298:E770-E778

AMERICAN JOURNAL OF PHYSIOLOGY
Endocrinology and Metabolism

Persistent enhancement of GSIS in previously Norepinephrine-infused fetuses.

After birth, transient hyperglycemia might exaggerate insulin secretion!



Xiaochuan Chen et al. J Endocrinol 2017;232:285-295

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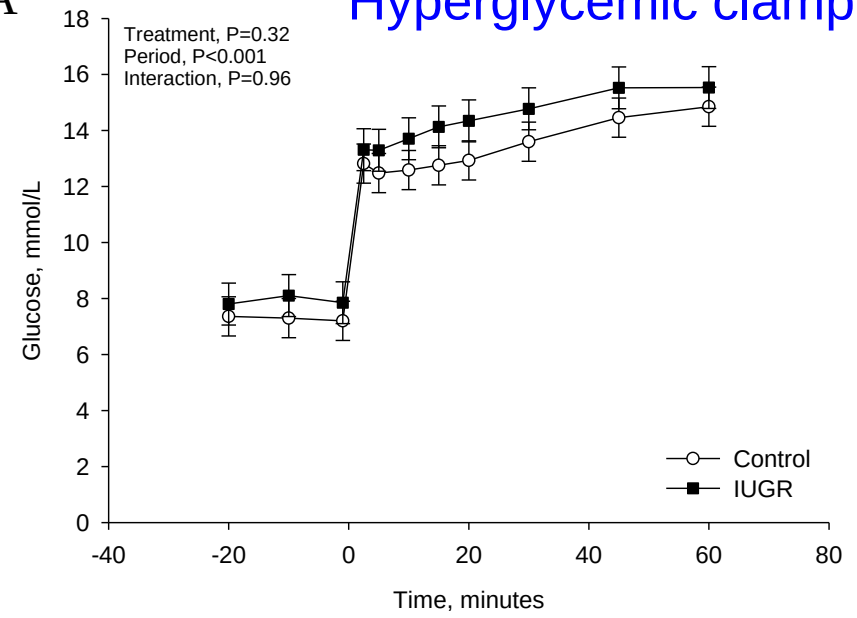

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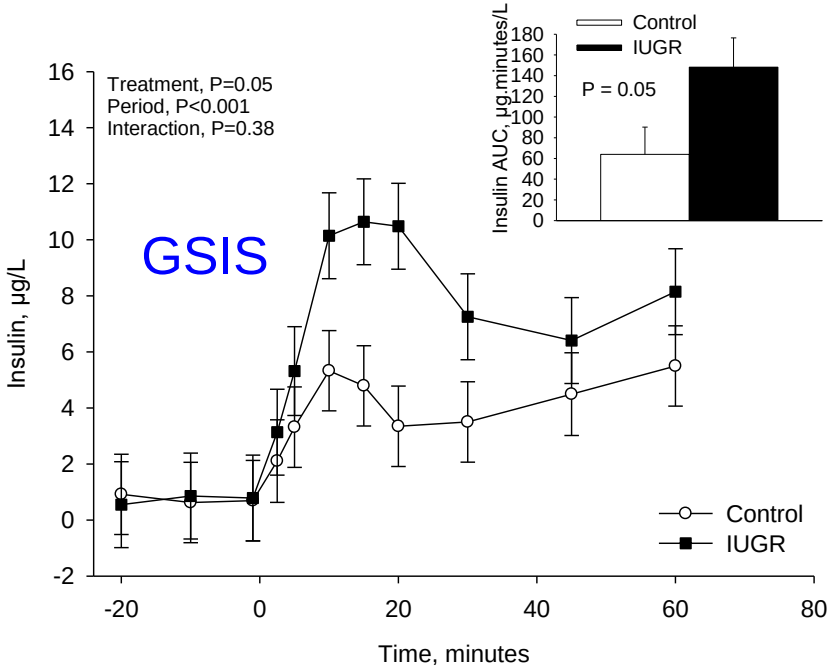


And increased glucose-stimulated insulin secretion (GSIS) in former IUGR lambs persists up to 4 weeks post term delivery.

Camacho, Frank, Hay, Limesand.
Unpublished data.

Perisistent hyperinsulin-like Hypoglycemia in IUGR infants: a significant clinical problem explained with basic research.

a. **greater head/brain to body/liver ratio, so greater body weight-specific glucose utilization rate. Persists well after birth.**

b. **increased peripheral tissue glucose uptake capacity, from increased or at least maintained glucose transporters. Persists well after birth.**

c. **increased fractional insulin secretion and susceptibility to anapleurotic metabolic stimulation of insulin secretion. Persists well after birth.**

d. **Increased insulin secretion after reduction of catecholamine suppression of insulin secretion. Persists well after birth.**

Treatment of IUGR infants with persistent hypoglycemia

1. Check glucose concentrations frequently.
2. Treat with IV dextrose initially to prevent seriously low glucose values, but do NOT increase glucose values suddenly or maintain at a higher than normal level.
3. Start early and frequent (q 2 hours) enteral feedings.
4. Maintain frequent feeding. Just like infants with FAO disorders. It is difficult for families to do, but it works.
5. Do not send home until this approach is successful for 2-3 days and for at least 4 hours between feedings.
6. Educate families about how to avoid lack of feeding and signs of hypoglycemia.

So what do we do?

Treatment of Hypoglycemia

- **Anticipation and prevention** are the key elements of intervention and management.
- **Early identification of an infant at risk** for developing hypoglycemia and institution of prophylactic measures to prevent its occurrence constitute the best treatment for this disorder.
- In infants in whom hypoglycemia does occur, the **treatment goals are two-fold:**
  - to **return** the glucose concentration to normal levels and, once normalized
  - to **maintain** levels within the normal range.
- **Develop and stick with a rational protocol.**

Guidelines for Glucose Monitoring

- **Healthy full-term infants born after an entirely normal pregnancy and delivery and who have no clinical signs do not require monitoring of glucose concentrations.**

- **Breastfed infants have lower glucose concentrations, but higher ketone concentrations, suggesting that these conditions are normal and that lower glucose concentrations (perhaps by 10 mg/dL) might apply to breastfed infants—in general, healthy appearing breastfed infants do not require glucose monitoring.**

Complications of Asymptomatic Hypoglycemia

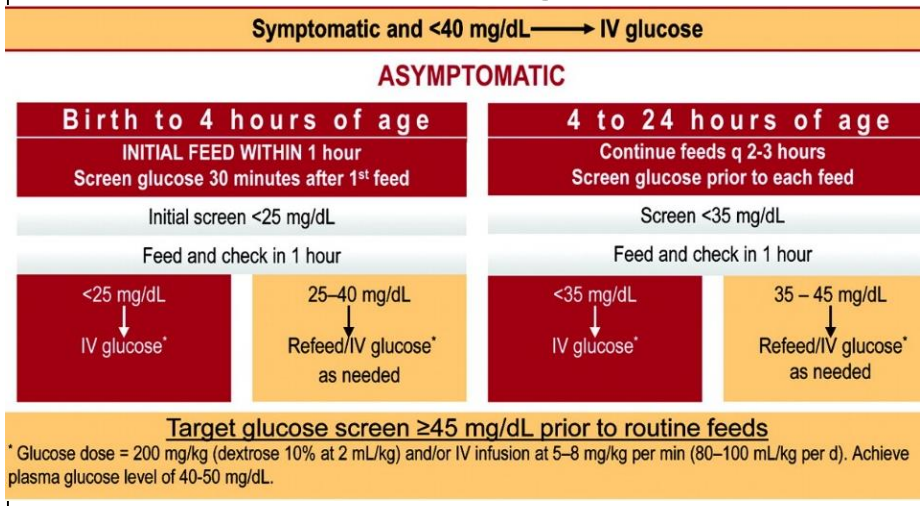
Most neonates with asymptomatic hypoglycemia have a normal Neurodevelopmental outcome,

although minor abnormalities, such as learning disabilities and abnormal EEGs (without seizures) occasionally have been reported (individual exceptions to every rule--!).

Most adverse outcomes occur in high risk infants who have other reasons for adverse outcomes—don't blame all adverse outcomes on associated low glucose values.

What glucose concentration targets to use for diagnosing and treating asymptomatic hypoglycemia?

American Academy of Pediatrics



Birth – 4 hrs, keep >25 mg/dL, aim for >40 mg/dL with feeding; IV if <25 mg/dL despite feeding.

4-24 hrs, keep >35 mg/dL, aim for >45 mg/dL with feeding, IV if <35 mg/dL despite feeding.

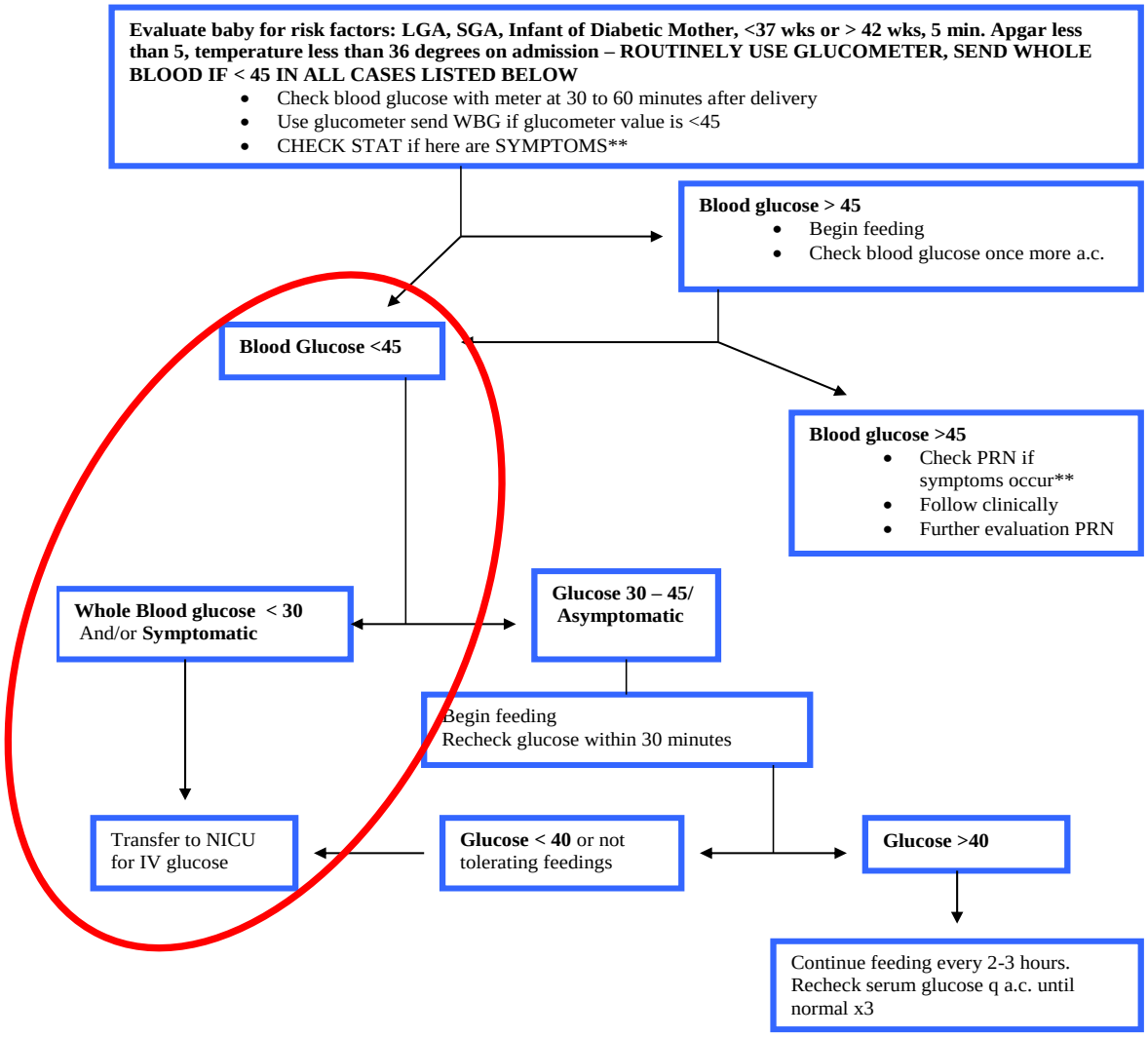
Pediatric Endocrine Society

Target >50 mg/dL in the first 48 hours.

Target >60 mg/dL if on IV Dextrose at any time or age >48 hours.

Neither of these recommendations/guidelines is based on evidence from controlled studies--!!

Guidelines for Management of Newborns at Risk for Hypoglycemia



Previously used University of Colorado Hospital Newborn Nursery and NICU Guidelines—

High incidence of transfer to NICU, usually because subsequent values <45 mg/dL and infants became "symptomatic".

****Symptoms of Hypoglycemia**
lethargy, poor feeding, irritability, emesis, tachycardia, jitteriness, cyanosis, seizures, respiratory distress, apnea, temp instability, tachypnea, pallor

But then along came oral dextrose gel.

Harris DL, et al. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:2077-83.

Neonates 35-42 weeks' gestation, < 48-hr-old, and at risk of hypoglycemia, randomly assigned (1:1) to **40% dextrose gel 200 mg/kg** or **placebo gel** rubbed into the buccal mucosa.

Dextrose gel reduced the frequency of treatment failure (glucose concentration did not increase or even decreased) compared with placebo (16 [**14%**] **vs** 29 [**24%**]; relative risk 0·57, 95% CI 0·33-0·98; p=0·04).

No serious adverse events.

Three (3%) babies in the placebo group each had one blood glucose concentration of 0.9 mmol/L (16 mg/dL).

Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study). Hegarty JE, et al. PLoS Med 2016;13(10):e1002155. PMID 27780197 PMCID PMC5079625

IDMs, Late Preterms, SGA, or LGA infants (or other risk factors).

40% dextrose at one of two doses (0.5 ml/kg = 200 mg/kg, or 1 ml/kg = 400 mg/kg), **either once at 1 h of age or followed by three additional doses of dextrose** (0.5 ml/kg before feeds in the first 12 h) or to corresponding placebo groups.

Primary outcome: hypoglycemia (<2.6 mM) in the first 48 h. Secondary outcomes included admission to a NICU, admission for hypoglycemia, and breastfeeding at discharge and at 6 wk.

Compared to infants randomized to placebo,

The risk of hypoglycemia was lowest in infants randomized to a single dose of 200 mg/kg dextrose gel.

Infants who received any dose of dextrose gel were less likely to develop hypoglycemia than those who received placebo.

NICU admission for hypoglycemia less common in infants randomized to dextrose gel.

Rates of breastfeeding were similar in both groups.

Adverse effects…uncommon and not different between groups.

McKinlay CJ, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507-1518.

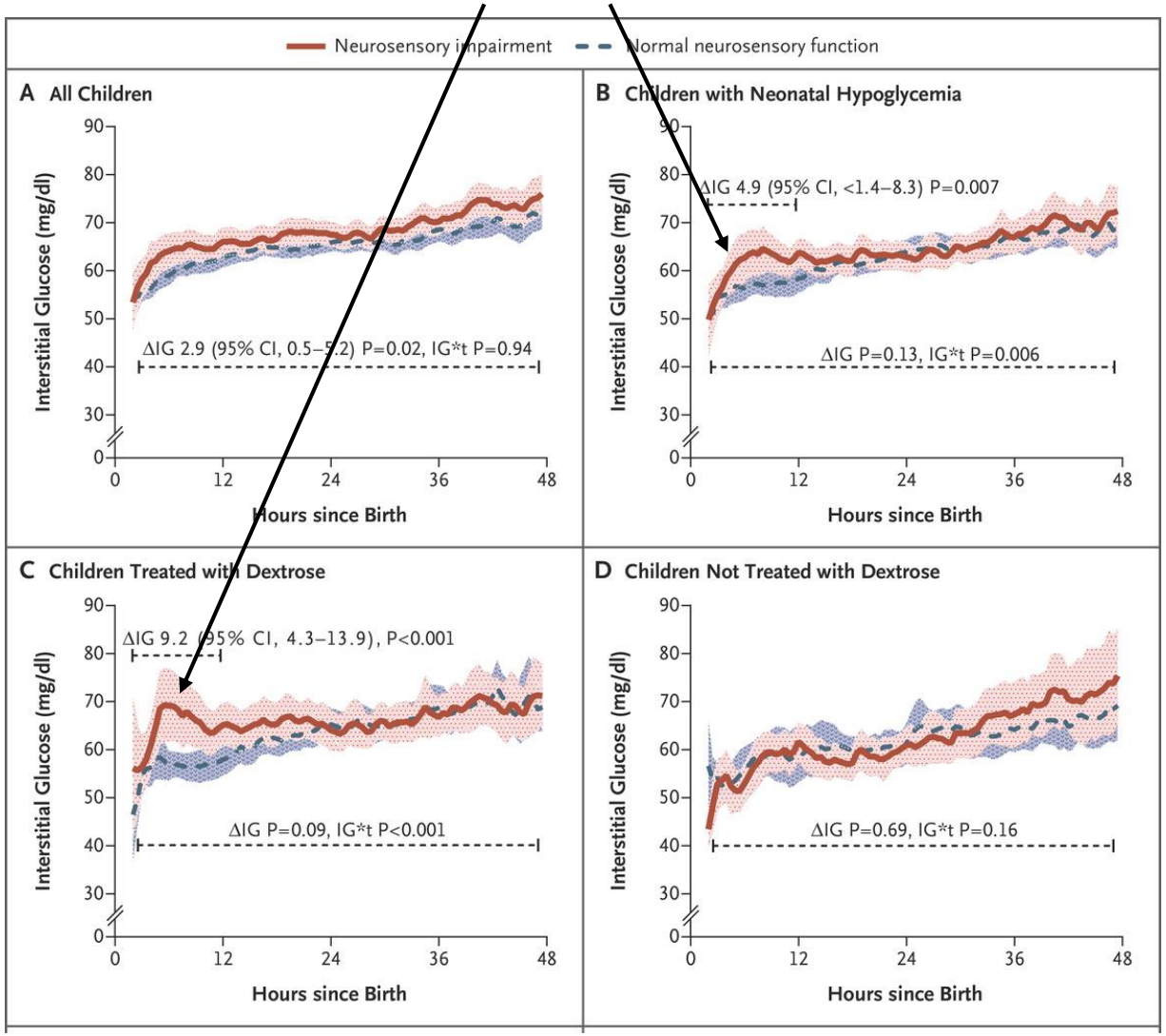
Prospective cohort study involving 528 neonates with a gestational age of at least 35 weeks who were considered to be at risk for hypoglycemia (IDM, LGA, SGA, late preterm); all were treated to maintain a blood glucose concentration of at least 47 mg/dL (2.6 mmol per liter).

Hypoglycemia, when treated to maintain a blood glucose concentration of at least 47 mg/dL, was not associated with an increased risk of the primary outcomes of neurosensory impairment and processing difficulty.

Risks were not increased among children with unrecognized hypoglycemia (a low interstitial glucose concentration only).

The lowest blood glucose concentration, number of hypoglycemic episodes and events, and negative interstitial increment (area above the interstitial glucose concentration curve and below 47 mg per deciliter) also did not predict the outcome.

But, a more rapid increase in glucose concentration and highly variable values after treatment were associated with neurosensory impairment.



Infants with hypoglycemia

Infants treated with oral dextrose

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

However--two year outcomes were equivalent between dextrose gel and placebo treated infants.

(neurosensory impairment, developmental delay, cerebral palsy, Bayley III composite, executive function, Brief-P index, vision)

	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

All NS

Harris DL, et al. J Pediatr 2016;170:54-59.

Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. **Cochrane Database Syst Rev 2016:CD011027 PMID 27142842:** 312 infants—Auckland; Ireland.

Infants treated with 40% dextrose gel—

- **had an average estimated rise in blood glucose concentration following dextrose gel was 0.4 mmol/L (7 mg/dL).**
- **less likely to be separated from their mothers for treatment of hypoglycemia**
- **more likely to be exclusively breast fed after discharge**
- **had no evidence of adverse effects during the neonatal period or at 2 years' corrected age.**

Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycemia.

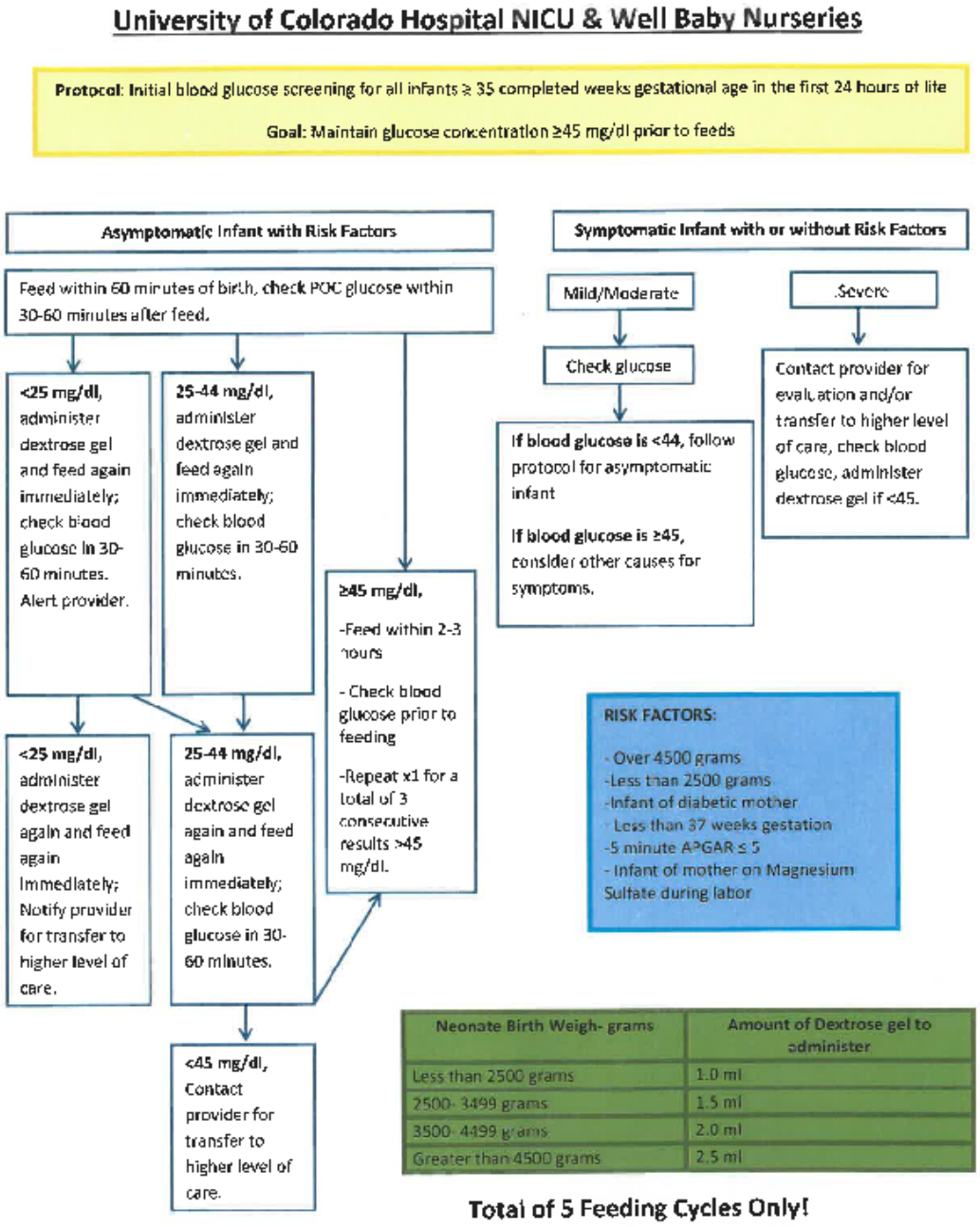
Harris DL, et al. What happens to blood glucose concentration after oral treatment for neonatal hypoglycemia? J Pediatr 2017. PMID 28709629

227 infants with hypoglycemia (blood glucose <46.8 mg/dL, 2.6 mmol/L)
Blood glucose concentrations were measured (glucose oxidase) within 90 minutes after randomization to dextrose or placebo gel plus feeding with formula, expressed breast milk, or breast feeding.

- **Increase in blood glucose concentration was 11.7 (10.4-12.8) mg/dL**
- Increase not affected by breast feeding or expressed breast milk
- **Breast feeding associated with reduced requirement for repeat gel treatment** (OR = 0.52; 95% CI 0.28-0.94; *P* = .03).

Conclusions: Treatment of infants with hypoglycemia with dextrose gel or formula is associated with increased blood glucose concentration and breast feeding with reduced need for further treatment.

Dextrose gel with breast feeding should be considered first-line oral treatment of infants with hypoglycemia.



New UCH Newborn Nursery and NICU Guidelines—

Started January 2017

Almost completely stopped NICU admission for “low glucose not responsive to early feeding”.

Oral Dextrose Protocol

At risk infants only: SGA, Late Preterm, LGA, IDM, low Apgar

Feed by 60 minutes after birth. Check glucose in 30-60 mins.

For Asymptomatic infants--

If <25 mg/dL, administer oral dextrose gel, re-feed, check again, if still <25 mg/dL, consider NICU and IV dextrose.

If 25-45 mg/dL, same pattern, consider NICU and IV dextrose if glucose falls to <25 mg/dL despite feeding.

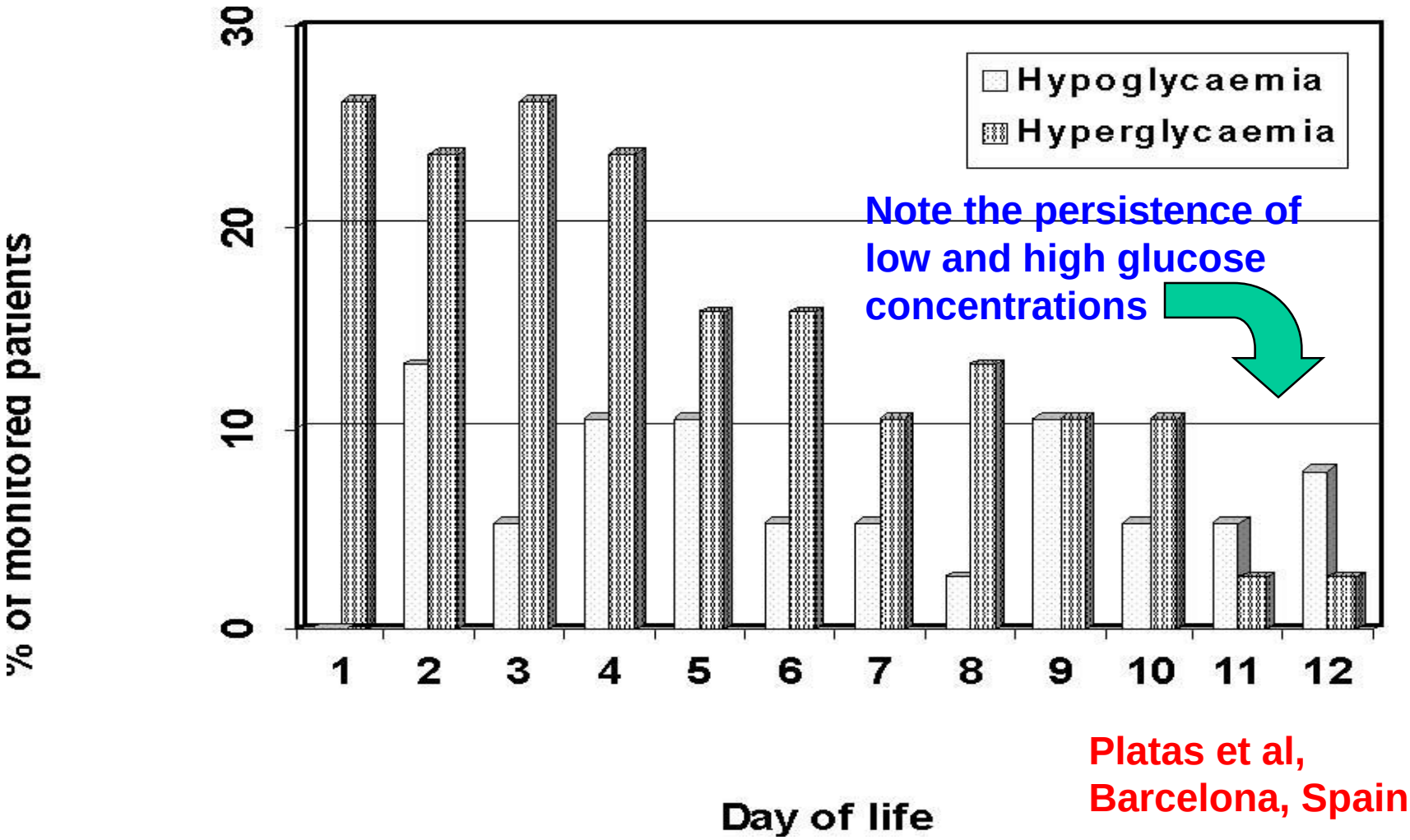
If >45 mg/dL, feed, check glucose before feeds, add oral dextrose gel if glucose falls to <45 mg/dL despite feeding.

For Symptomatic infants—

Mild to moderate and infant can feed, use oral dextrose gel and frequent feeding; only send to NICU if this fails.

Severe symptoms—urgent transfer to NICU, but if delayed, try oral dextrose gel.

Is it time for
Continuous Glucose Monitoring?



Platas et al,
Barcelona, Spain

Continuous Glucose Monitoring??
Not ready for primetime.

1. No information about the clinical significance of episodes of low interstitial glucose concentrations and which, if any, should be treated, or in which infants.

2. Which glucose concentration (and of what duration) should be used as the lower limit threshold for clinical management? (same old problem, just more often)

3. Danger that continuous glucose monitoring might be incorporated into clinical practice without critical assessment and might result in many more infants being treated than would be necessary.

Continuous Glucose Monitoring??
The time to start is now.

Need for **studies** to clarify relationships between continuous glucose concentrations, symptomatic hypoglycemia, response to treatment, associated medical conditions, and neurodevelopmental outcomes.

The importance of such studies must be balanced with the delay in implementing this technology and its potential to detect serious, recurrent hypoglycemia in patients with hyperinsulinemic hypoglycemia and other metabolic disorders.

Learning from medical legal claims.

Risk factors: low or borderline low birth weight (<2.5 kg)

Presenting clinical signs: abnormal feeding behavior (especially feeding poorly after initially feeding well). Hypothermia next most common.

Likely deficits in care (most cases have more than one):

- Inaccurate point of care (near-patient) testing device
- Failure to assess risk factors, clinical signs, or causes
- Failure to take into account maternal concerns
- Failure to commence blood glucose monitoring for infants with identifiable risk factors
- Discharge of infants with risk factors or clinical signs without assurance that feeding was sufficient to prevent hypoglycemia
- Multiple types of delays in treating and/or following up cases

Hawdon JM, Beer J, Sharp D, et al. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F110-F115.

Summary

1. Plasma glucose concentrations in any neonate of any gestational or postnatal age should be above 45-50 mg/dL (2.5-2.8 mM) “most” of the time.

2. There is no evidence that transient values (minutes to an hour or so—duration is undefined !!) below these values are detrimental, but just don’t let them recur or especially get worse.

3. There is no evidence that asymptomatic hypoglycemia, even if recurrent or prolonged, is detrimental—just avoid such conditions, as treatment has no rational basis—yet.

4. Treat ASAP with IV glucose those infants with glucose concentrations that are severely low (<20 mg/dL [< 1.1 mM]), prolonged (>30 minutes), and associated with serious signs of encephalopathy (coma, seizures, hypothermia, feeding poorly after feeding well).

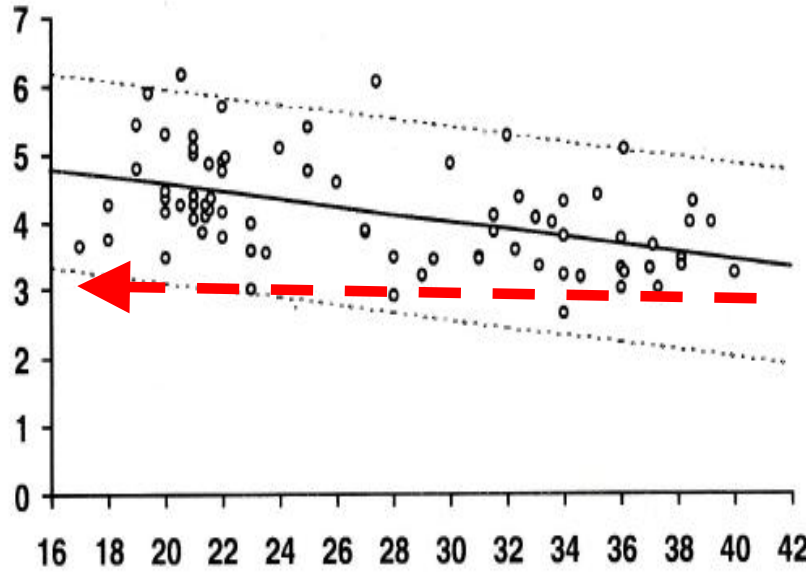
5. Do not allow recurrent hypoglycemia to recur, especially before discharge from the hospital.

Practical approach: remember that the lower limit glucose value in normal fetuses and term neonates is **~3.0 mmol/L (~54 mg/dL).**

Just keep glucose concentrations above this value most of the time.

Normal Fetus

>3.0 mM (54 mg/dL)



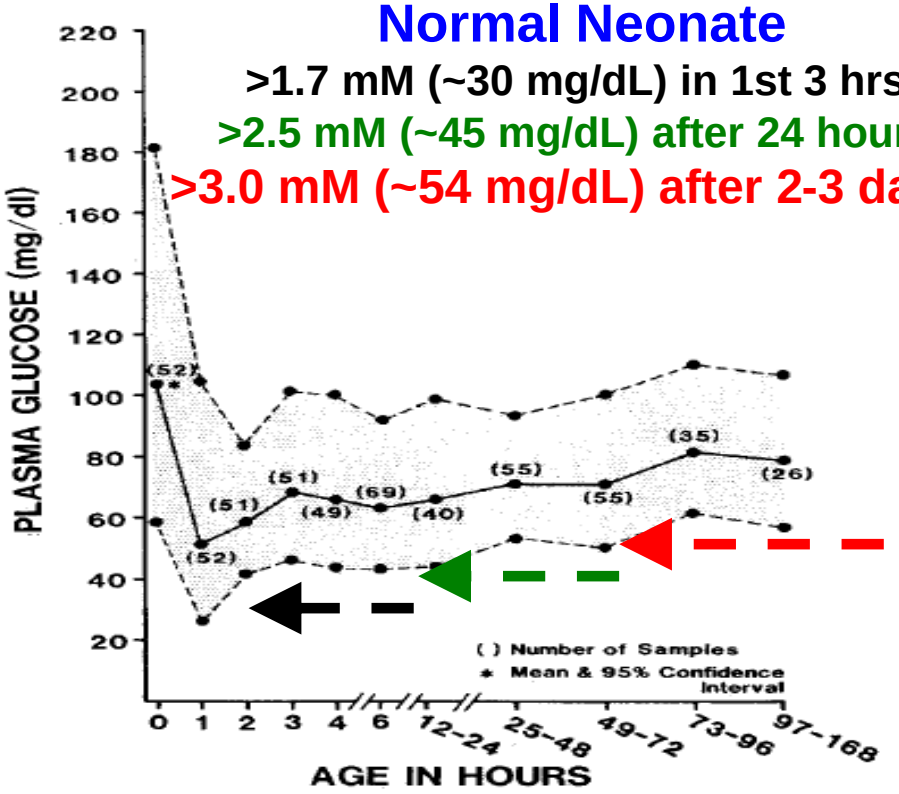
Marconi AM, et al., 1996

Normal Neonate

>1.7 mM (~30 mg/dL) in 1st 3 hrs,

>2.5 mM (~45 mg/dL) after 24 hours,

>3.0 mM (~54 mg/dL) after 2-3 days.



Srinivasan G, et al., 1986.

University of Colorado
Anschutz Medical Campus
School of Medicine

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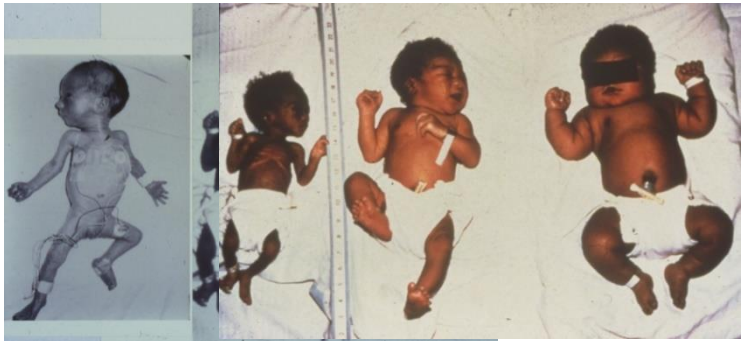

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