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Neonatal Hyperglycemia

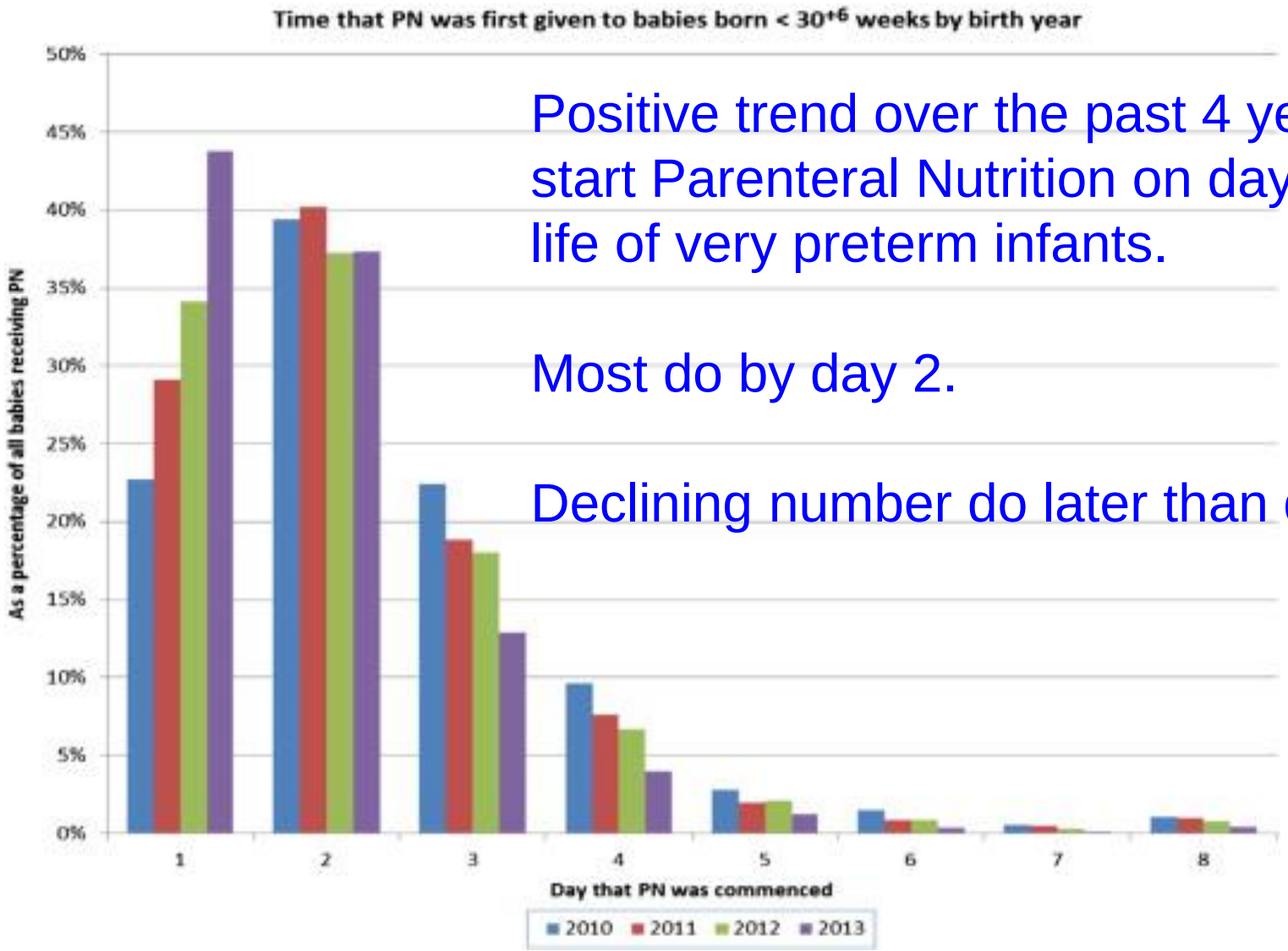
William W. Hay, Jr. MD

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



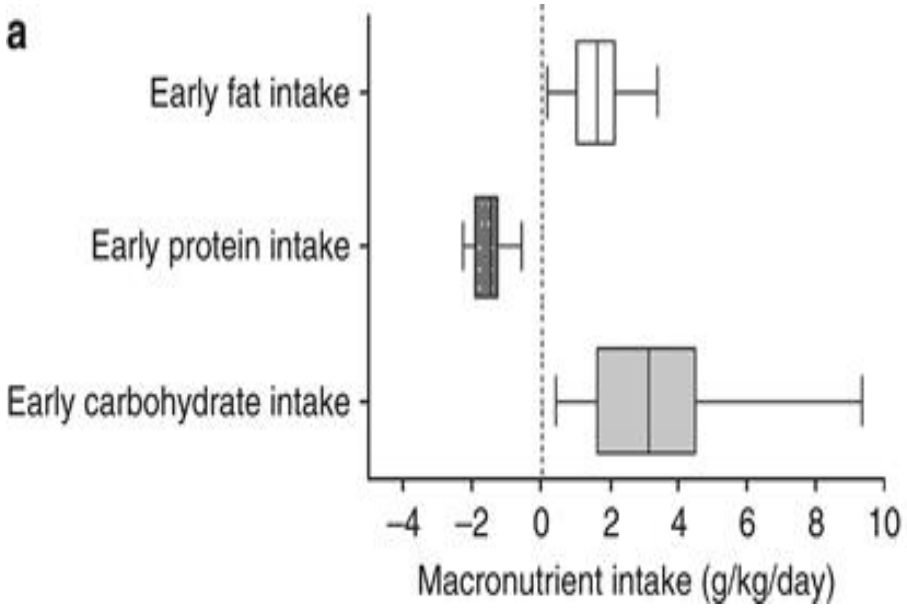
Positive trend over the past 4 years to start Parenteral Nutrition on day 1 of life of very preterm infants.

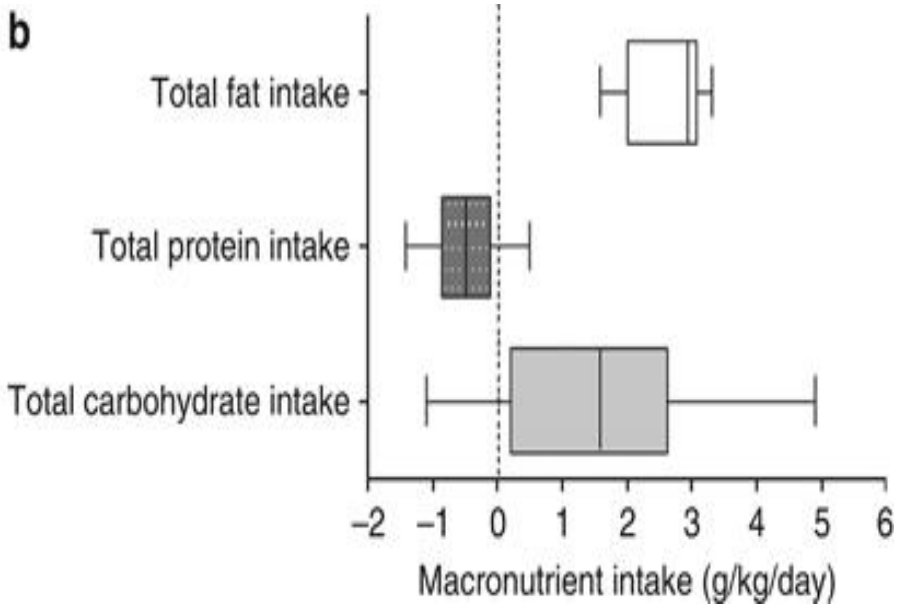
Most do by day 2.

Declining number do later than day 2.

Time that PN was first given to babies born before 30 + 6 weeks by birth year in all neonatal units in England and Wales. (N = 3646, 4047, 4090, 4123 in 2010, 2011, 2012 and 2013 respectively).

Uthaya S, Modi N. Practical preterm parenteral nutrition: Systematic literature review and recommendations for practice. Early Human Development, 2014





But, actual intake of nutrients has been weighted to energy, carbohydrate and lipid, not to protein, leading to problems of CHO and Lipid excess and protein insufficiency. Such a diet mix will lead to fatter, shorter, less muscular infants, and perhaps to neurological deficits.

V Vasu, E L Thomas, G Durighel, M J Hyde, J D Bell and N Modi. Early nutritional determinants of intrahepatocellular lipid deposition in preterm infants at term age. Int J Obes (Lond). 2013; 37:500-504.

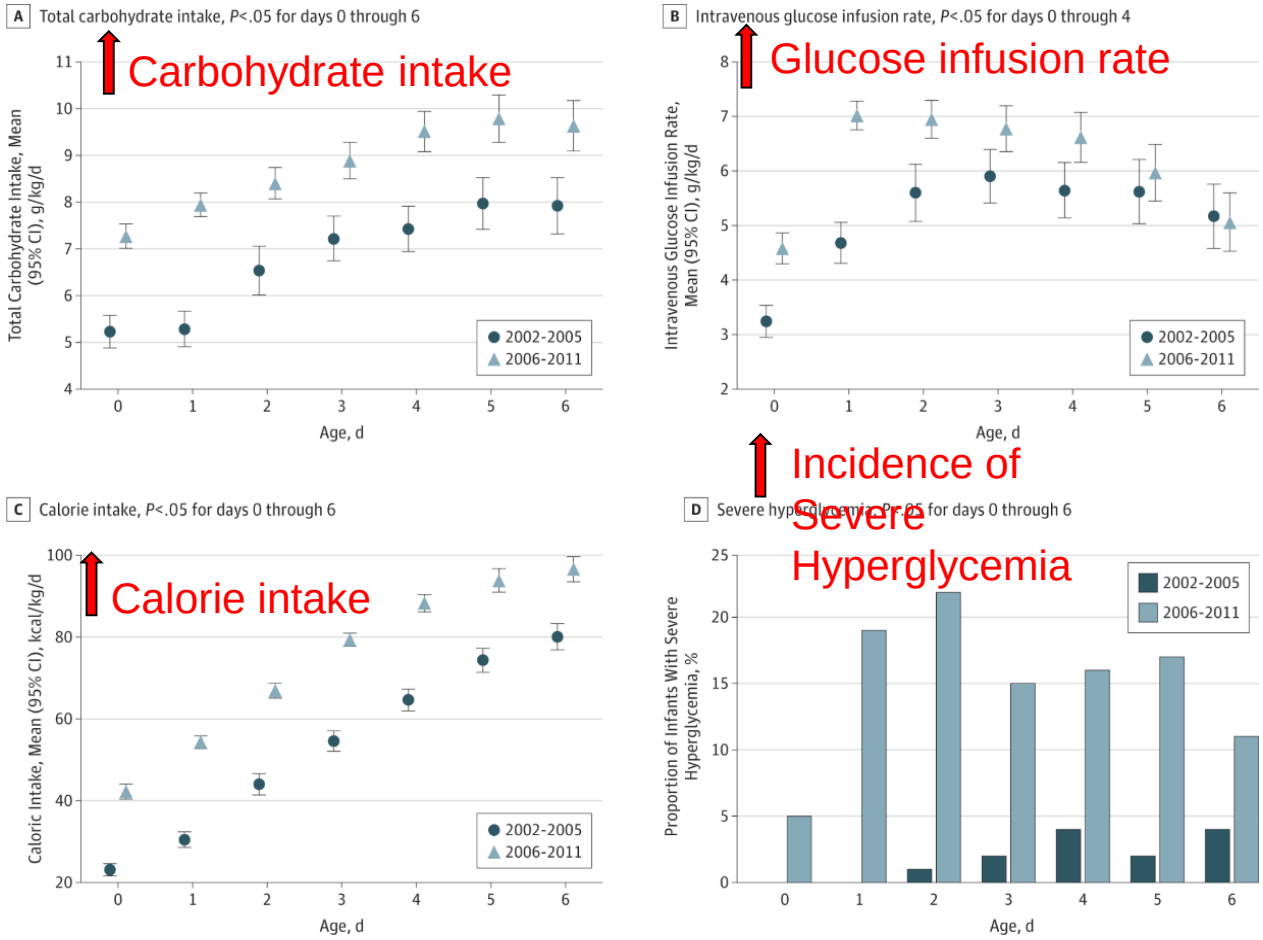
IV Glucose

Standard approach,
used/recommended by most:

- **6-8 mg/min/kg beginning at birth,**
- **increasing to 12-14 mg/min/kg for full IVN (~70-80 Kcal/kg/day),**
- **done sort of reflexively, without considering the degree of illness or other pathophysiology in the infant.**

What happens?

As a result, HYPERGLYCEMIA has become almost universal in recent years (2006-2011 ● vs. 2002-2005 ▲).



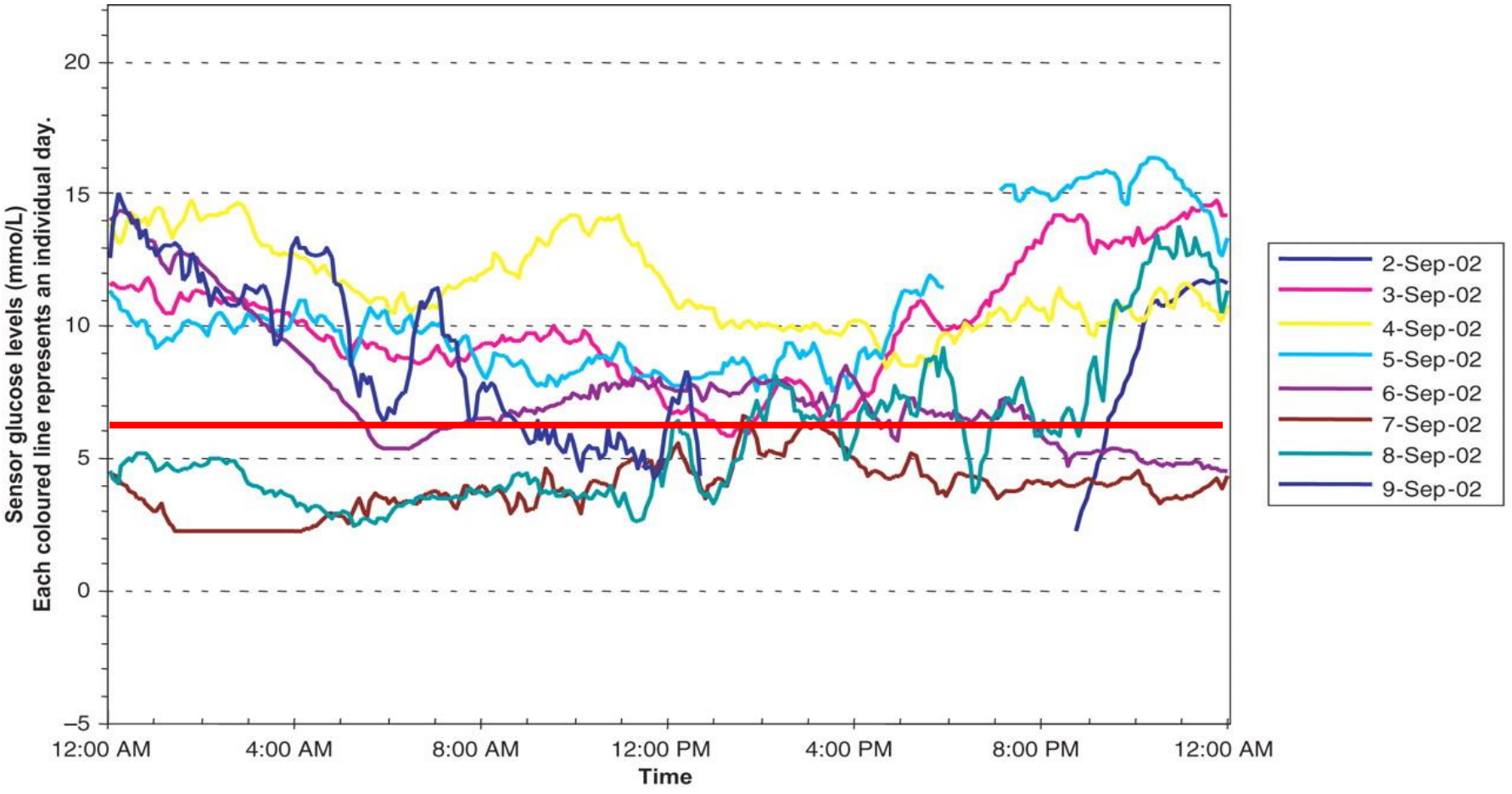
Severe hyperglycemia:

2 or more consecutive values of >216 mg/dL (12 mM/L) at least 3 hrs apart.

Highly (0.001) associated (marker or cause??) with death risk.

Stensvold HJ, et al., JAMA Pediatr. Published online, September 08, 2015.1-8

Continuous glucose monitoring profile from a very-low-birth-weight infant during the first week of life—highly variable and mostly high (>6mmol/L, uppler limit of normal human fetuses)..



Ogilvy-Stuart A L , Beardsall K. Arch Dis Child Fetal Neonatal Ed 2010;95:F126-F131

Other risks for hyperglycemia in neonates that compound higher than needed rates of IV glucose infusion

- Preterm birth, Low birth weight, and IUGR (OR 0.5)

  (less insulin secretion at lower gestational ages and in IUGR fetuses—fewer pancreatic ß-cells)

- Absence of enteral feedings

  diminished "incretins" that promote insulin secretion (already less in ELBWs)

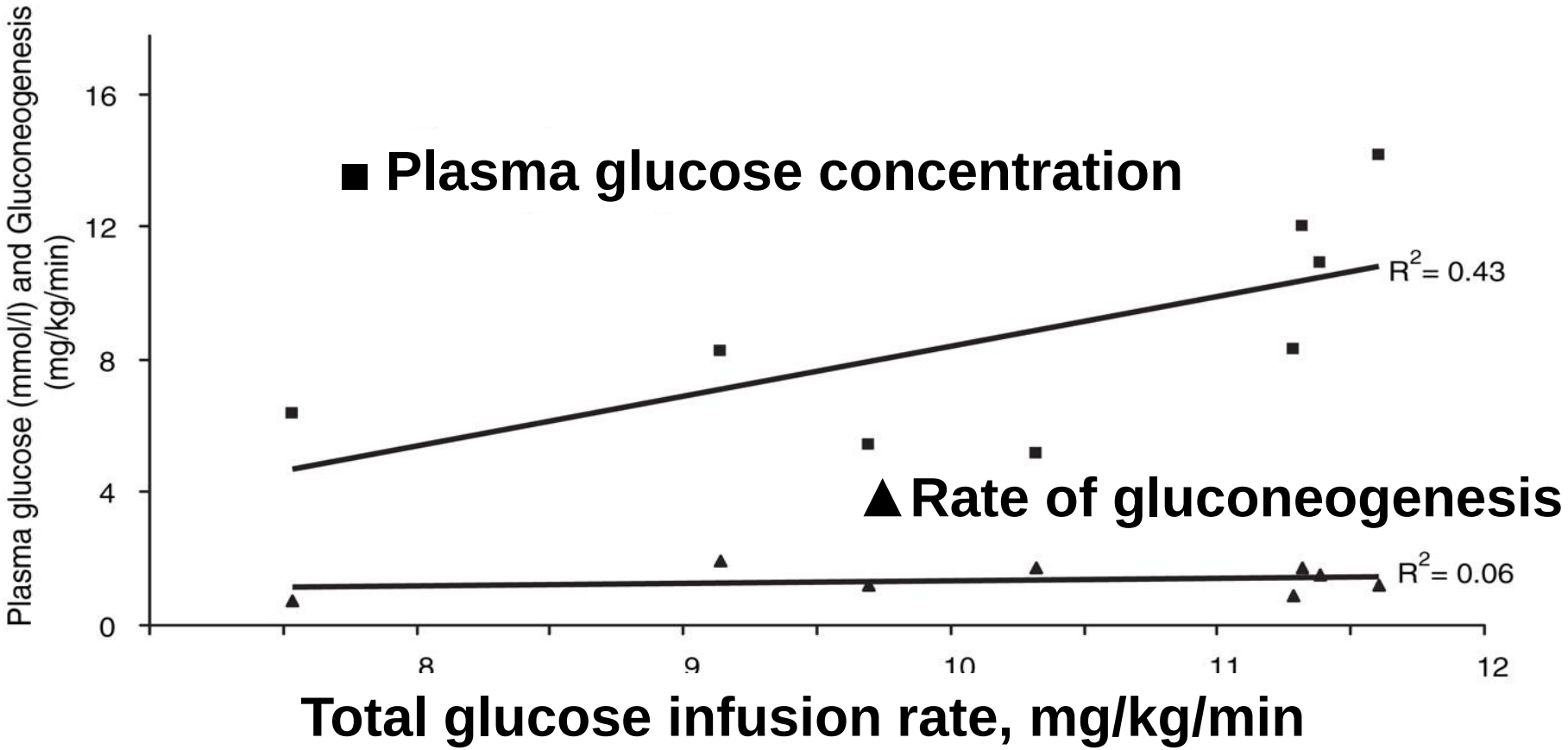
- Proven or suspected **sepsis**
- Increased catecholamine infusions and plasma concentrations
- Increased glucocorticoid concentrations

  (use of steroids, before/after birth; stress; sepsis)

- Early and high rates of IV lipid infusion (OR 1.11)
- **Persistent hepatic glucose production**

  (IUGR, hepatic insulin resistance. Preemies—usual causes)

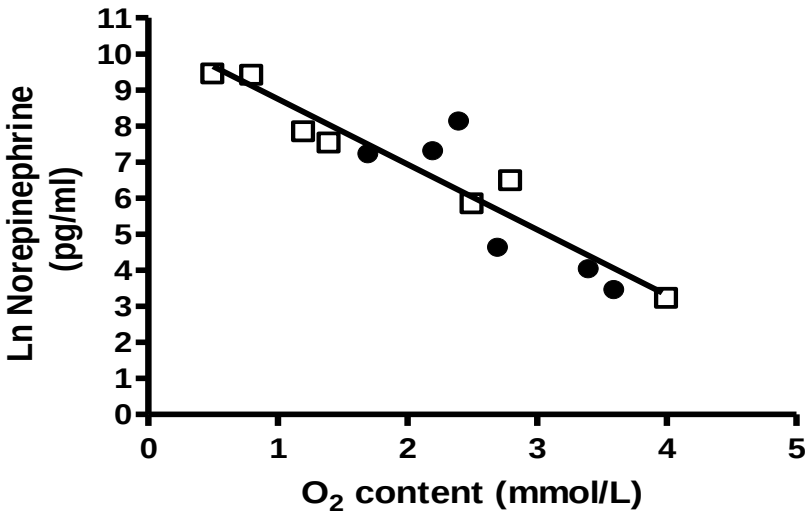
First, glucose production persists in newborns despite high glucose and insulin concentrations. As a result, glucose concentrations increase directly and linearly with any increase in IV glucose infusion rate.

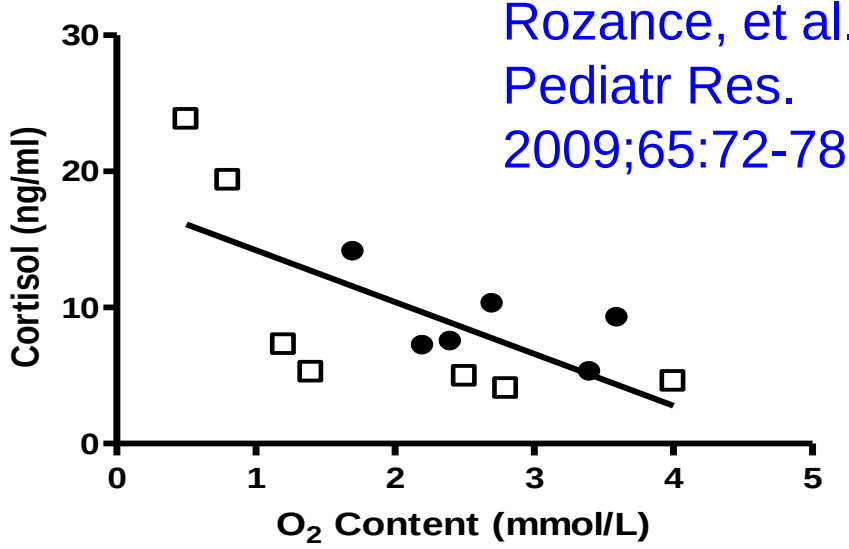


Chacko S, Sunehag A. Arch Dis Child Fetal Neonatal Ed 2010;95:F413-F418

FN

Then, because hypoxic-ischemic conditions lead to insufficient oxygen that leads to ↑ counter-reg. hormones that produce hyperglycemia!





Rozance, et al., Pediatr Res. 2009;65:72-78.

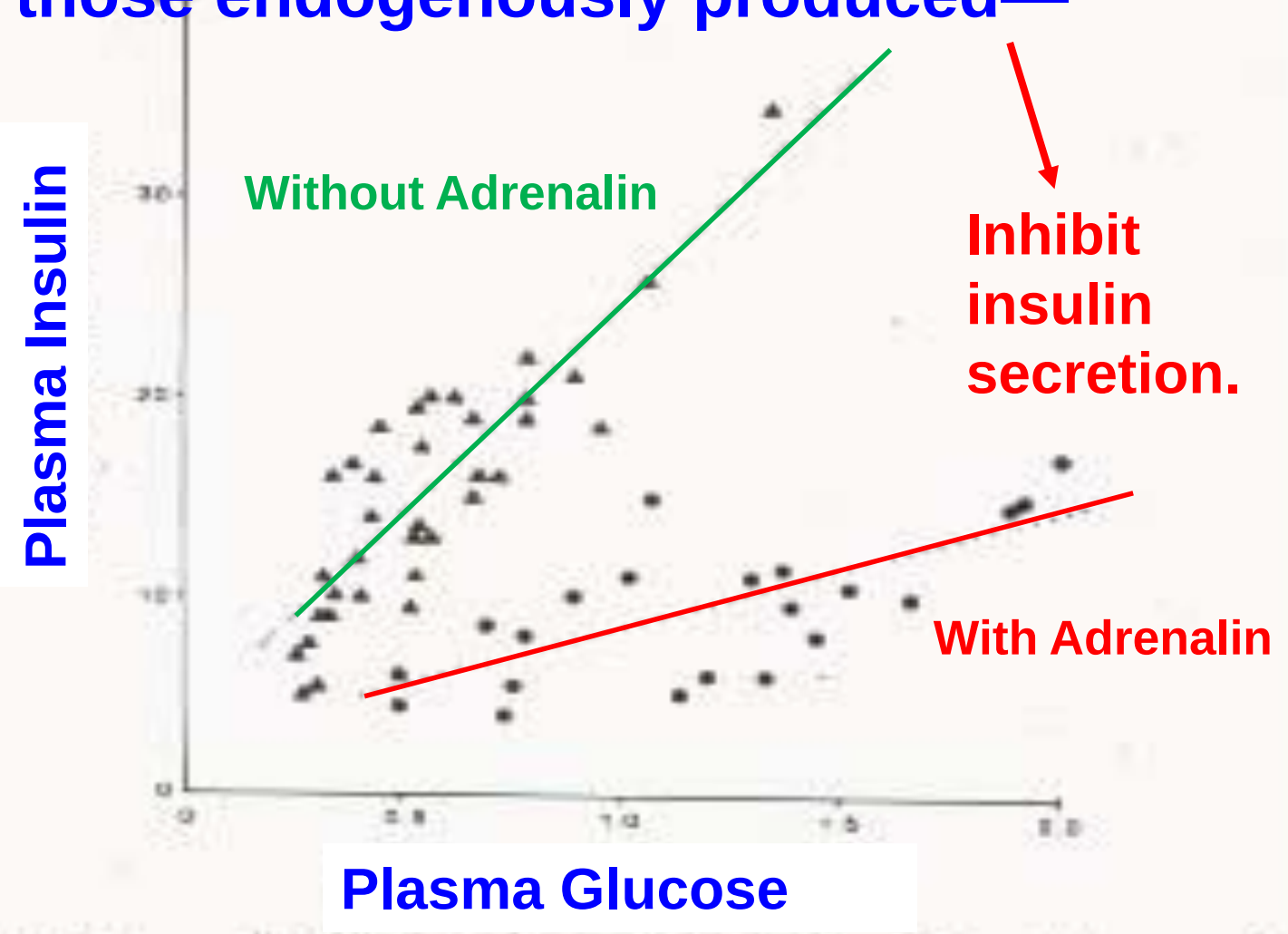
Hypoxia-ischemia → Increased catecholamines

Increased glycogenolysis
Decreased insulin secretion
Decreased insulin action
Increased protein breakdown

Hypoxia-ischemia → Increased cortisol

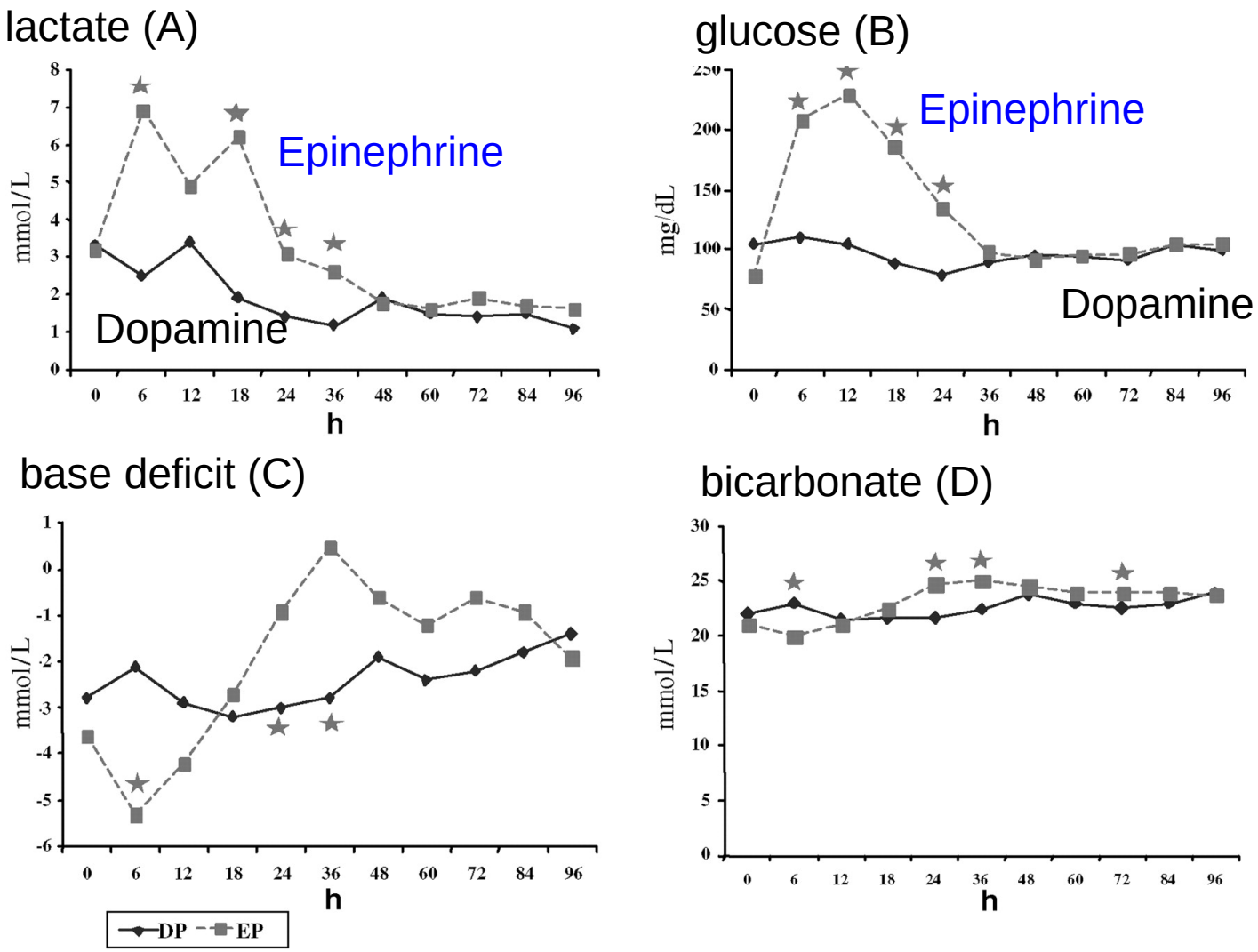
Increased gluconeogenesis
Increased protein breakdown
Decreased insulin secretion and insulin action.

And infused catecholamines do the same thing as those endogenously produced—



Fowden, Abigail L. "Pancreatic Endocrine Function and Carbohydrate Metabolism in the Fetus," in Perinatal Endocrinology, E. Albrecht and G.J. Pepe (eds.), Perinatology Press, 1985, p. 78.

Evolution of metabolic parameters in responders to Epinephrine and Dopamine: from baseline before giving the inotrope (time 0) and throughout the first 96 hours of life.



Valverde E, et al. (Seri I) Pediatrics 2006;117:e1213-e1222

PEDIATRICS®

And risk for hyperglycemia is further compounded by

Glucagon secretion–

promotes glycogenolysis (activates glycogen phosphorylase) and gluconeogenesis (activates PEPCK, especially when insulin is low)

Intravenous lipid infusion--

FFAs limit glucose oxidation competitively

Glycerol fuels gluconeogenesis *(Sunehag)*

FFA metabolic products (ATP, AcCoA, NADH) activate enzymes that promote gluconeogenesis *(Narkewicz and Girard)*

Hyperglycemia in IUGR infants.

a. Fewer pancreatic β-cells (mitotic arrest).

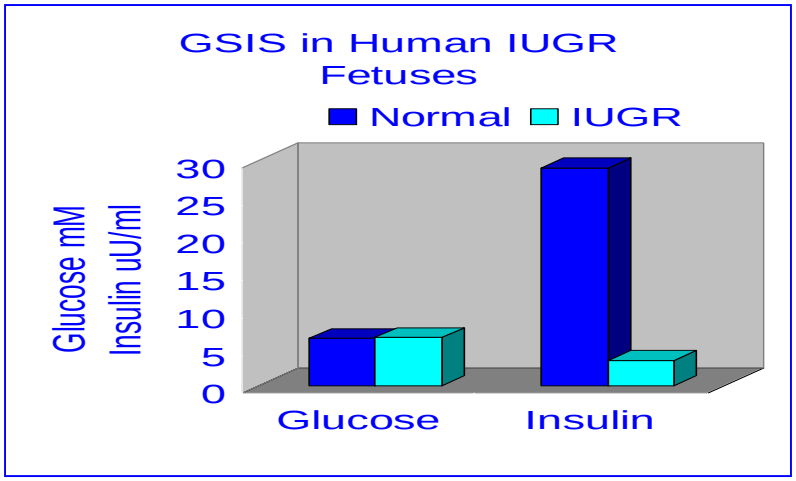
b. Reduced insulin production.

c. Suppressed insulin secretion by high catecholamines.

d. Hepatic insulin resistance and increased glucose production.

Pancreas Development and Insulin Secretion—both reduced in the IUGR fetus.

Human IUGR Fetuses: Reduced glucose-stimulated insulin secretion

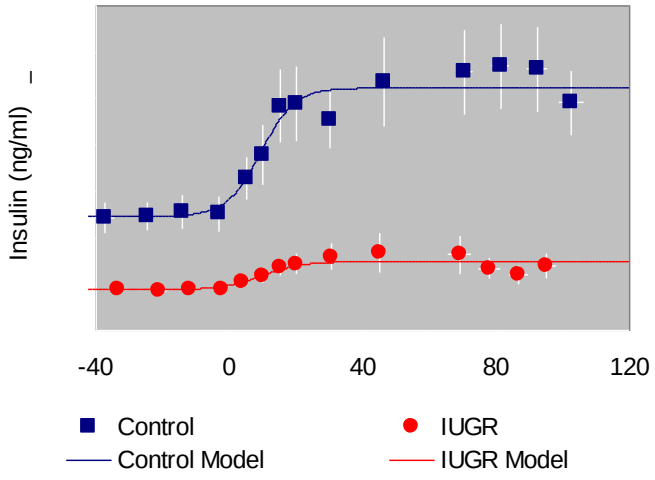


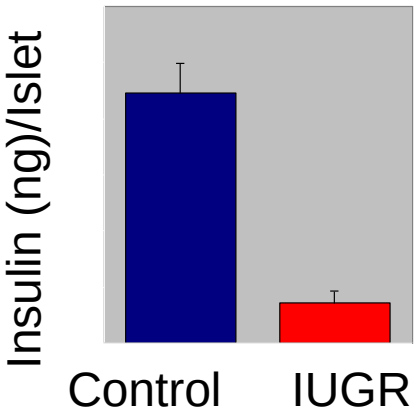
Nicolini et. al., 1990

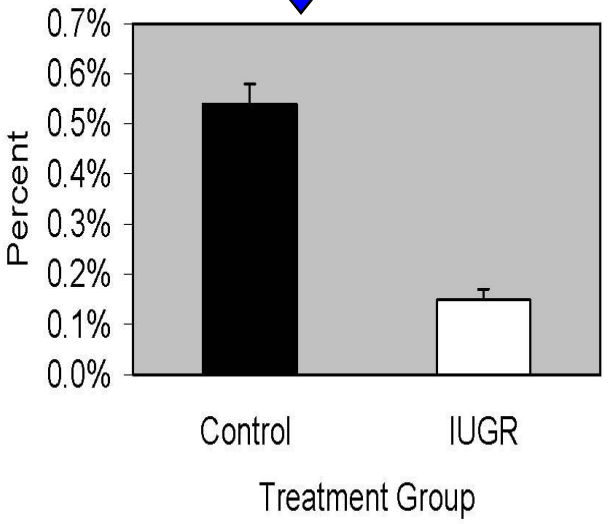
Glucose Stimulated Insulin Secretion is reduced at 133 dGA (90% of term) in IUGR fetal sheep, due to

Islet Insulin Content

and β-cell mitosis

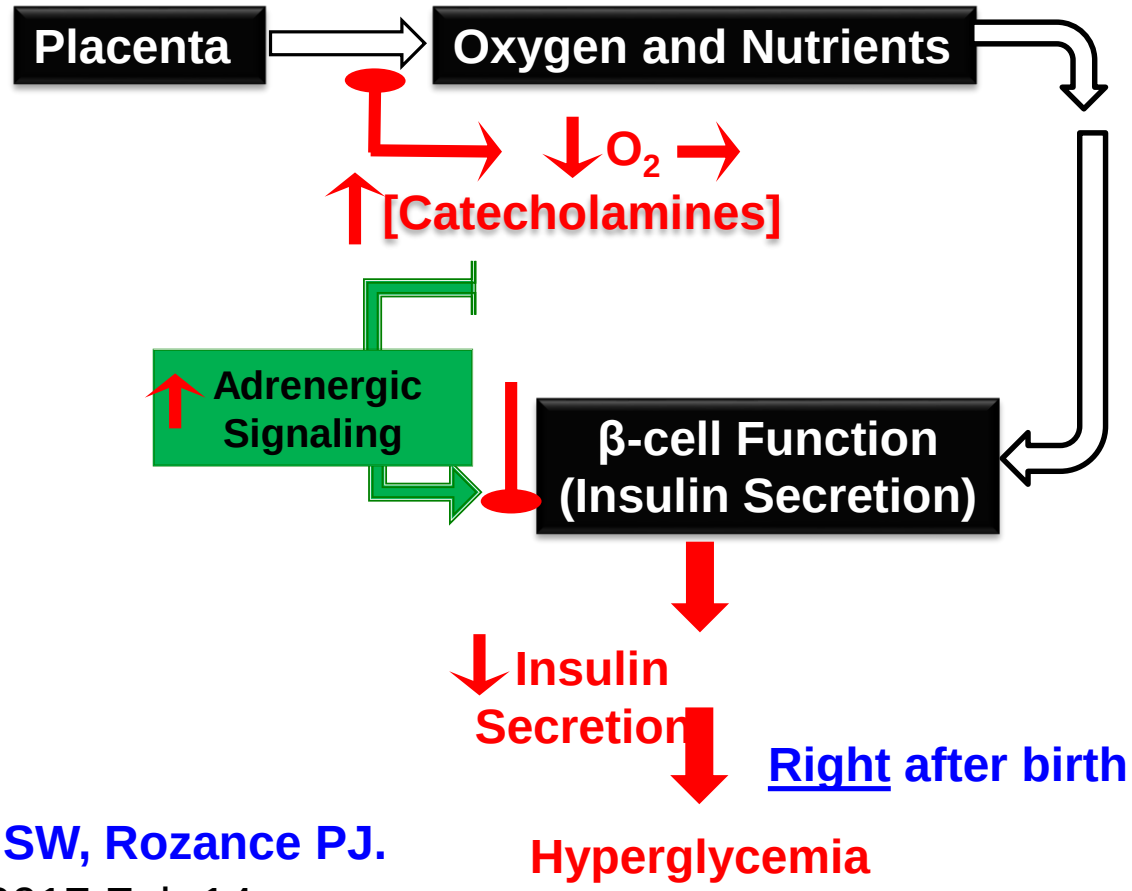






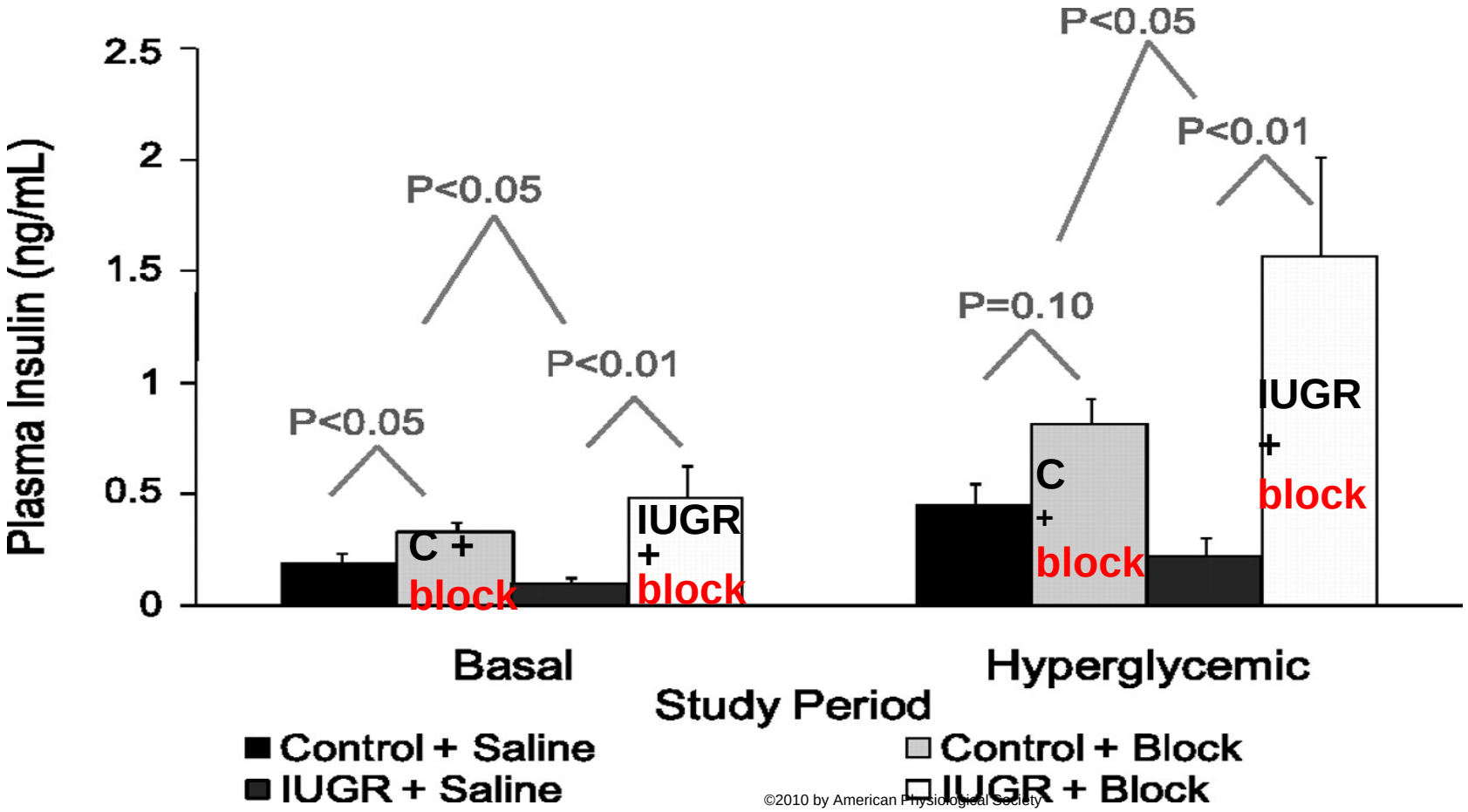
Limesand et al. 2006

Right after birth, with persistent stress, intermittent hypoxia, and catecholamine secretion, IUGR infants often develop hyperglycemia.



Limesand SW, Rozance PJ.
J Physiol. 2017 Feb 14.
PMID: 28194805

Furthermore, fetal insulin concentrations increase with blocking of catecholamines, proof that catecholamines suppress insulin secretion.



Sean Limesand's studies

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

Perinatal Transition in the "stressed", dextrose-infused, intermittently hypoxic, hypercatecholiminemic IUGR Neonate

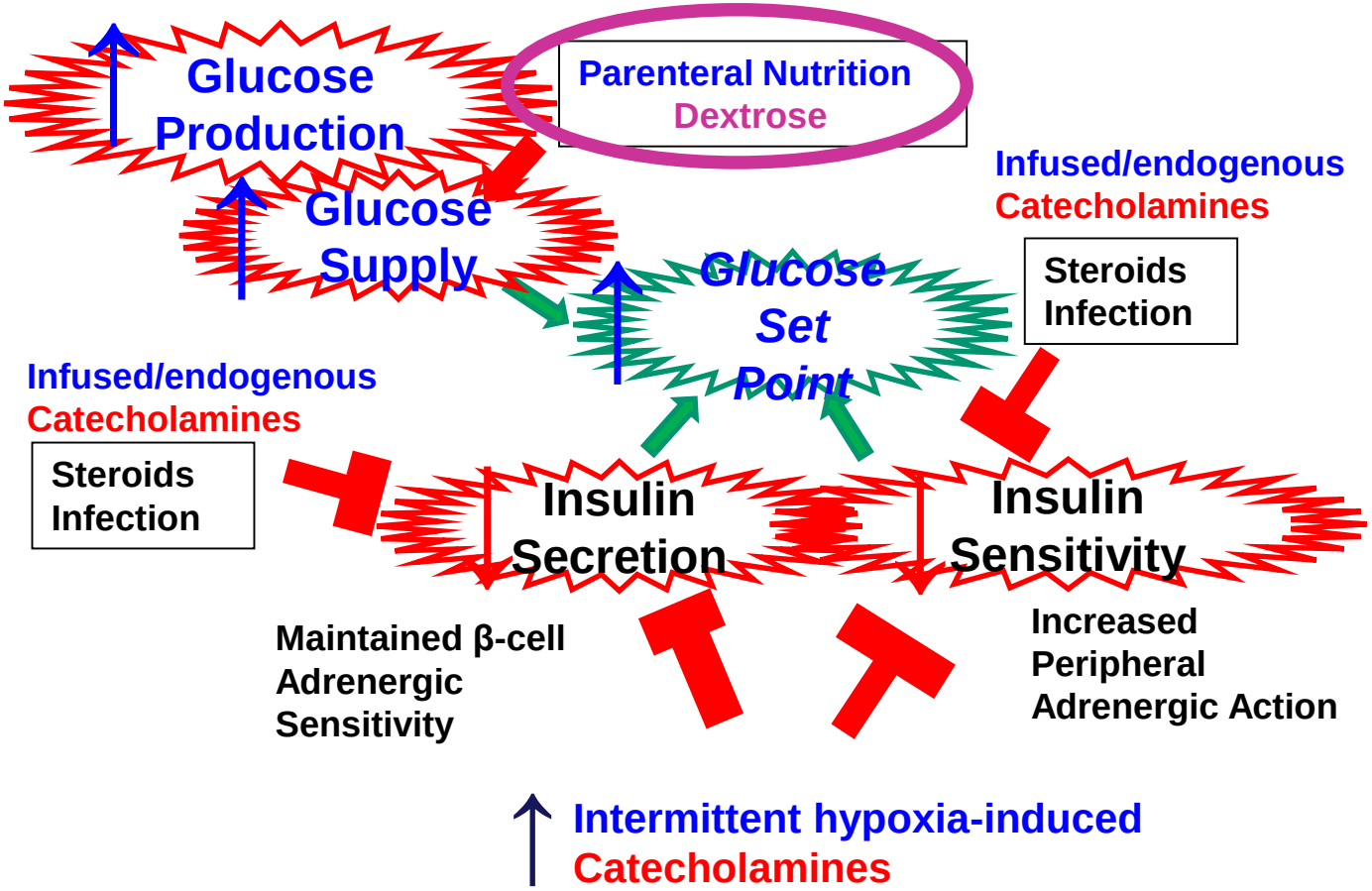


Figure adapted from
Paul Rozance,
unpublished

Thus, **Neonatal Hyperglycemia**

is common,

largely due to excess dextrose infusion
in the presence of stress responses.

But, is it a problem?

Complications of Neonatal Hyperglycemia—when maximal glucose oxidative capacity (>10-14 mg/kg/min) is exceeded.

Established adverse effects---

- ↑ Hyperosmolarity, polyuria, dehydration, acidosis, hyponatremia/hypokalemia, intracranial hemorrhage

  (almost always accidental—e.g., D75, not D7.5)
- ↑ energy expenditure (glucose-to-fat synthesis is energy expensive)
- ↑ oxygen consumption (and hypoxia)
- ↑ carbon dioxide production (and tachypnea)
- ↑ Fat deposition in excess of lean mass
- ↑ Fatty infiltration of heart and liver

Complications of Hyperglycemia in Adults

(difficult to dissociate from other problems, such as malnutrition and other pathophysiology)

1. Increased morbidity and mortality
2. Impaired immunity
3. Increased infection
4. Poor wound healing
5. Suppressed autophagy, cellular repair, organ recovery
6. Loss of skeletal and cardiac muscle

Evidence for such problems in hyperglycemic newborn infants is lacking or uncertain, most likely because no one has looked for it. If we did look, what would we see?

More recently documented adverse effects of Hyperglycemia:

mitochondrial stress from excess carbon load.

Bad Triad

- Increased cortisol/catecholamine levels
- Hyperglycemia (excess infusion, production)
- Increased Insulin

} Excess cellular glucose uptake

Excess mitochondrial carbon load

Mitochondrial fragmentation

Increased ROS production

Accumulation of mitDNA damage

Decreased energy producing capacity

Increased susceptibility to cell death

Cellular dysfunction

Oxidative stress

Molecular damage

Telomere shortening

Cell loss, ↑apoptosis

Energy deficiency

Systemic Inflammation

↘

Consequences?

Adapted from: Picard, M. *et al.* (2014)
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2014.22

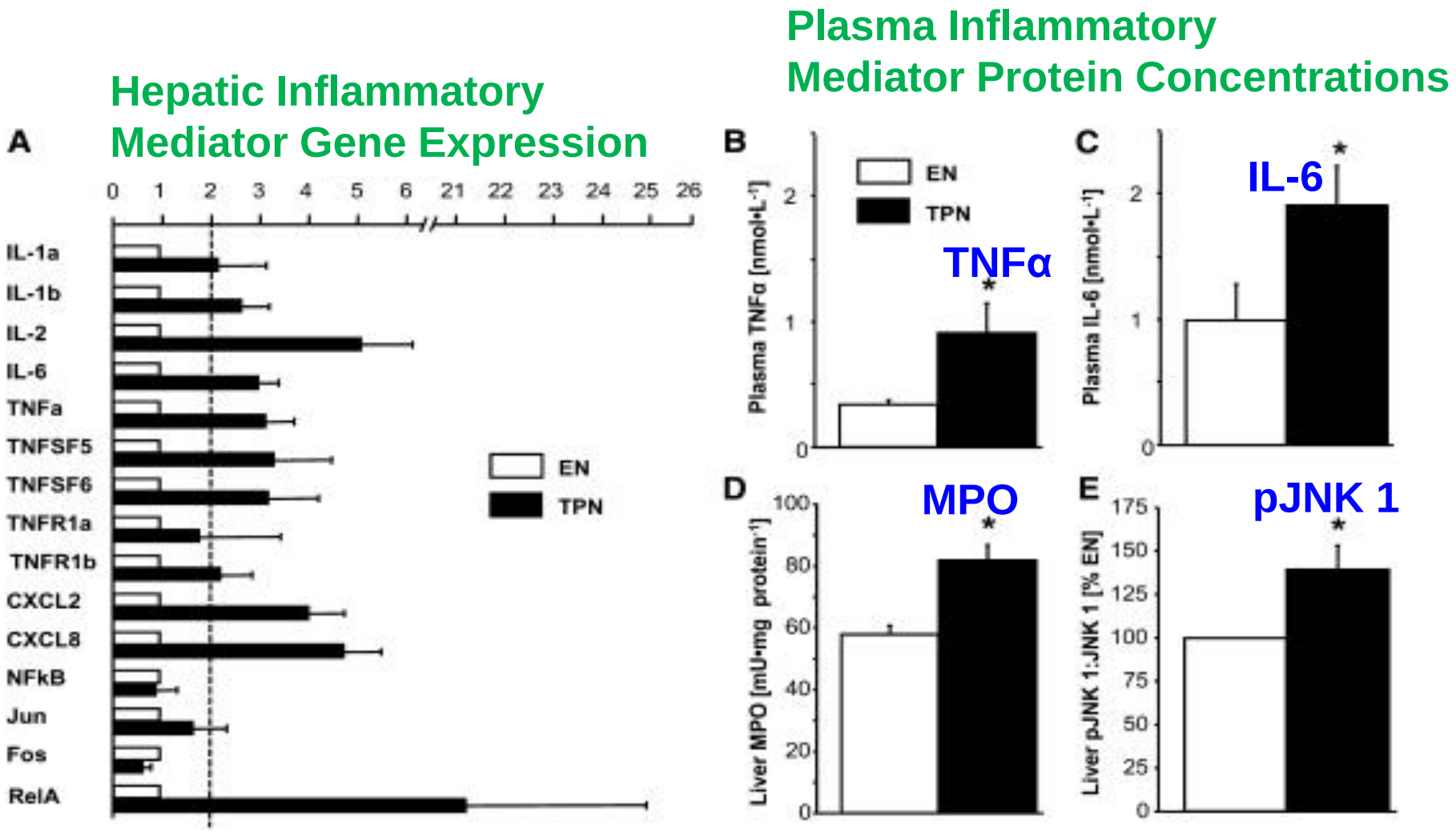
Excess glucose---increased mitochondrial carbon load, producing ↑ cell glucose uptake and ROS production—unanticipated adverse outcomes.

Bacteria thrive with excess glucose, leading to worse infections and death of the organism. So—in the NICU, where bacterial infections are more common as causes of serious sepsis, keep plasma glucose in the normal to low normal range.

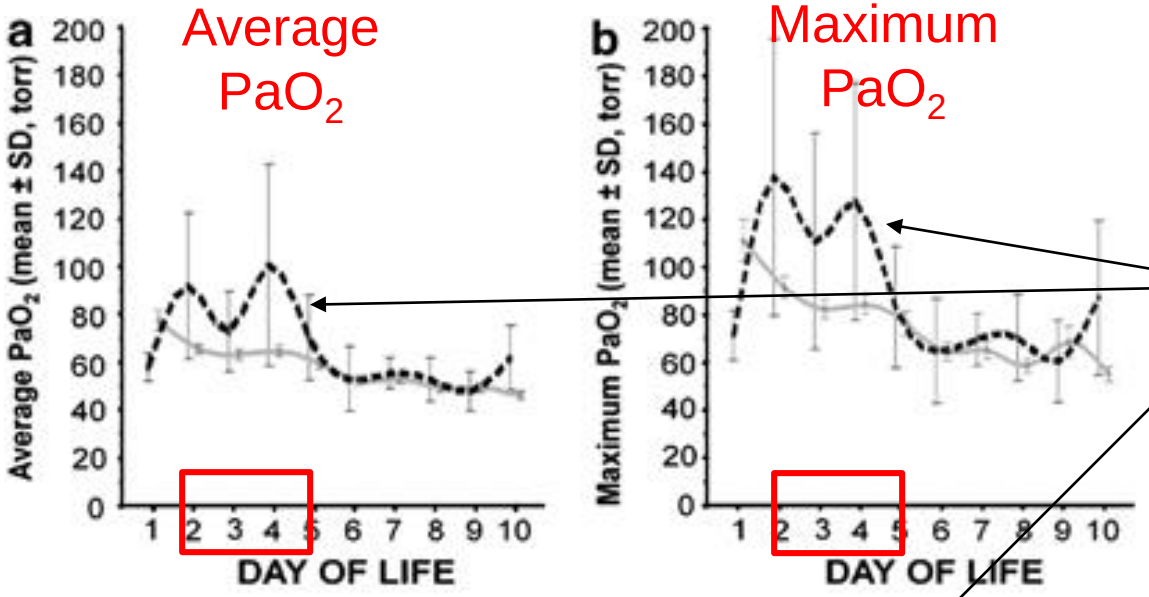
Viruses do the opposite, so if an infant has a proven virus infection, glucose supply might not be as bad.

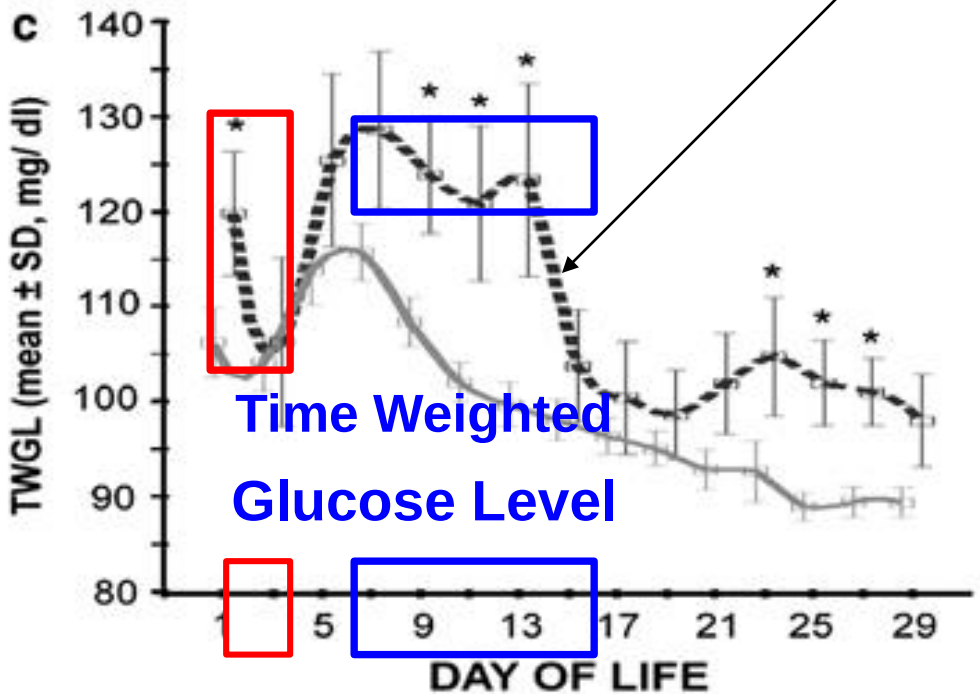
Wang A, Huen SC, Luan HH, Yu S, Zhang C, Gallezot JD, Booth CJ, **Medzhitov R**. Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation. Cell. 2016 Sep 8;166(6):1512-1525

TPN-induced hepatic and systemic inflammation? Perhaps from hyperglycemia?



Studies in piglets: Stoll B, et al. J Nutr 2010;140:2193-2200.



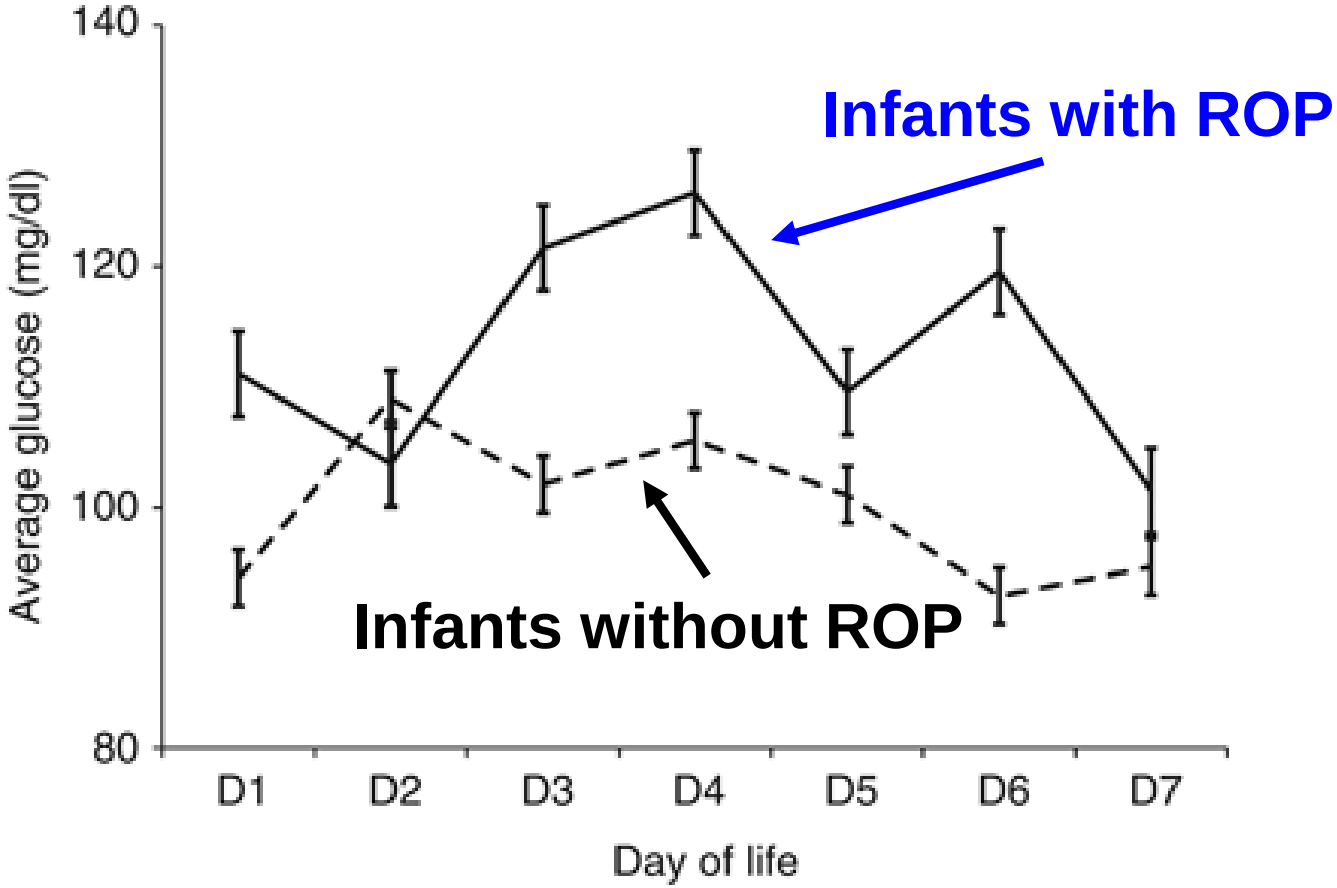


High overall glycemic status is *associated* with the development of **severe ROP**, **during** and **following** **hyperoxic** conditions.

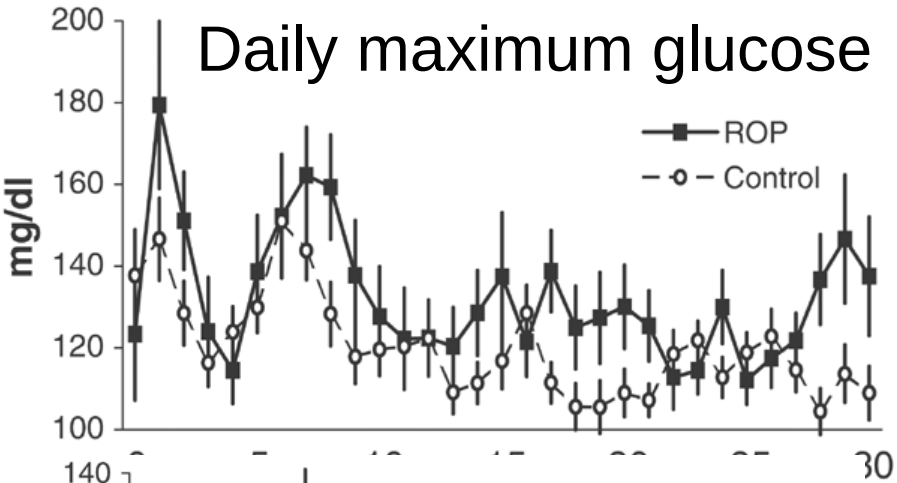
Chavez-Valdez R, et al. J Perinatology, 2011

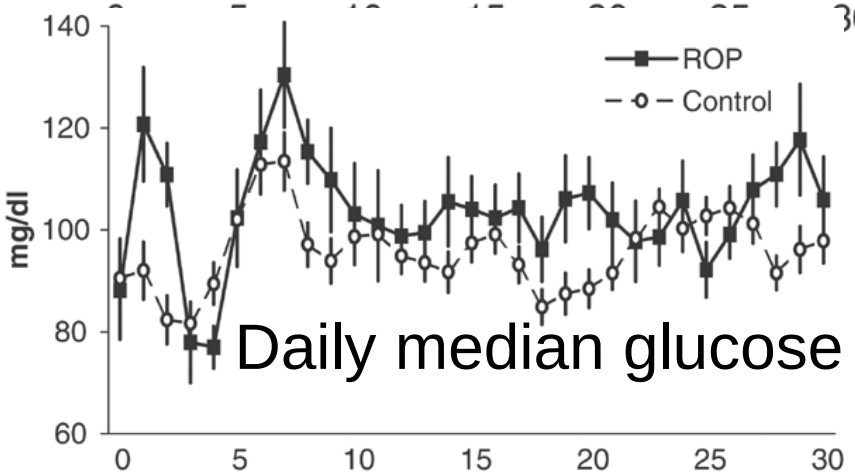
Insulin might make this worse by promoting glucose oxidation and ROS production, while Amino Acids might limit this by promoting IGF-1 production [Hellström], which appears protective against ROP.

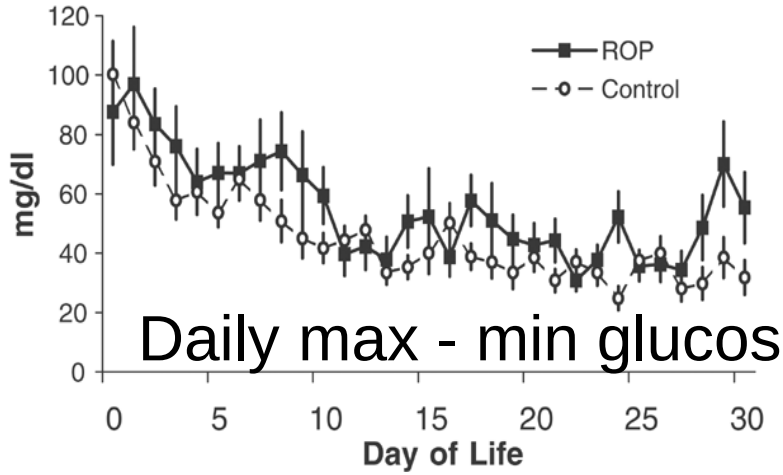
Greater number of infants with ROP who had sustained higher glucose concentrations.

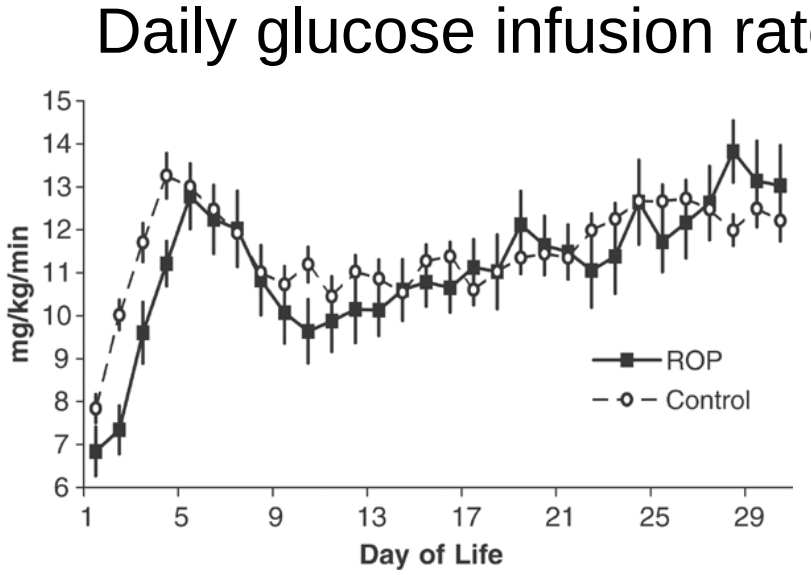


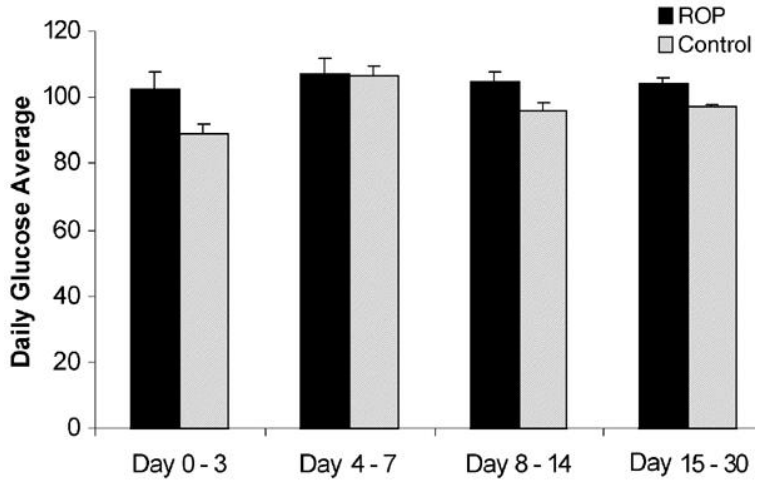
L Mohsen, M Abou-Alam, M El-Dib, M Labib, M Elsada and H Aly
A prospective study on hyperglycemia and retinopathy of prematurity. *Journal of Perinatology* (2014) **34,** 453–457





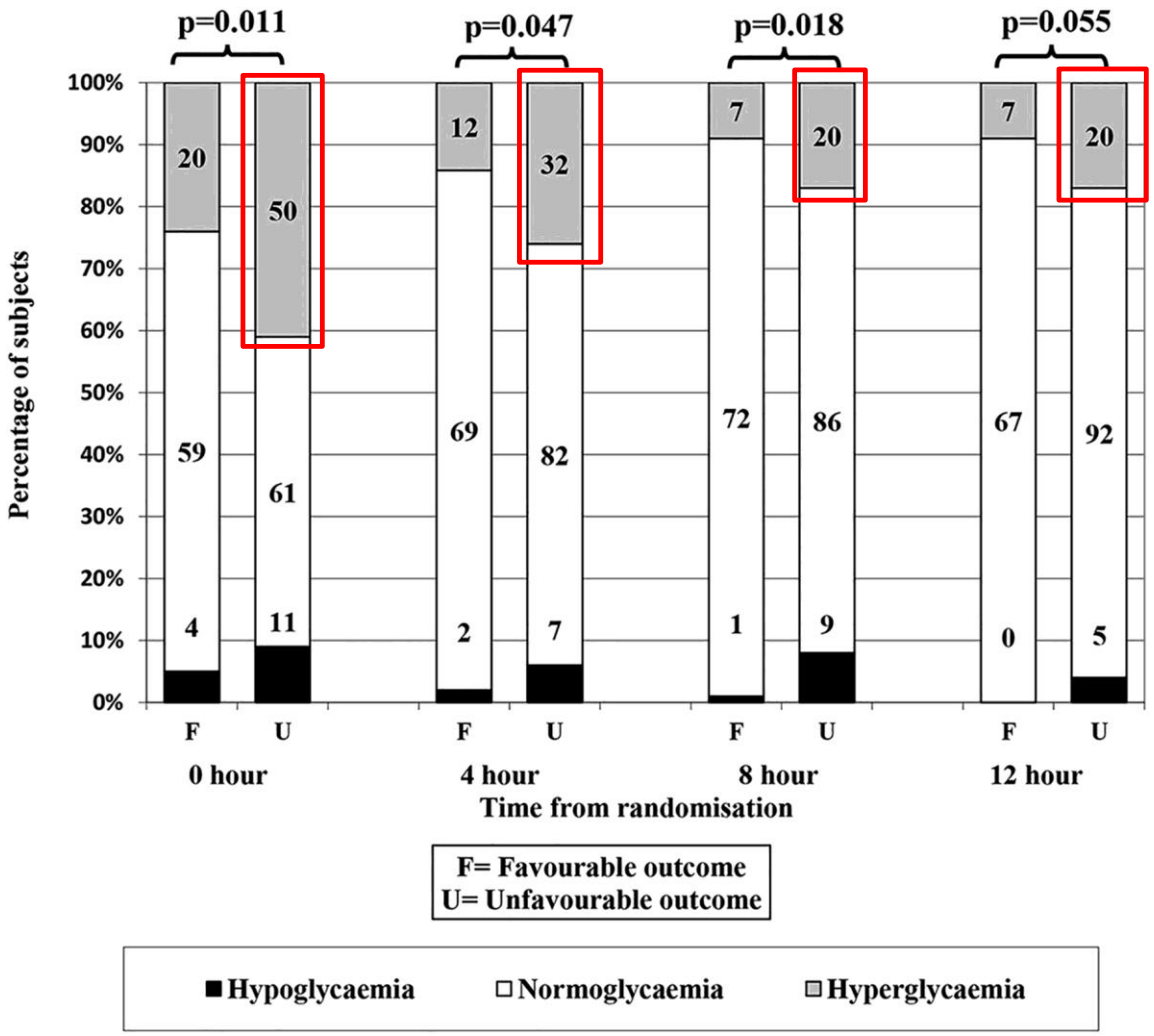






Garg R, et al. Hyperglycemia and Retinopathy of Prematurity in Very Low Birth Weight Infants. *J Perinatology* (2003) **23,** 186–194

Distribution of glucose values at each time point during the first 12 h stratified by favourable versus unfavourable primary outcome.



At every time point in the 1st 12 hours, hyperglycemia produced more unfavorable outcomes in infants with Hypoxic Ischemic Encephalopathy.

Sudeepta K Basu et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed doi:10.1136/archdischild-2015-308733

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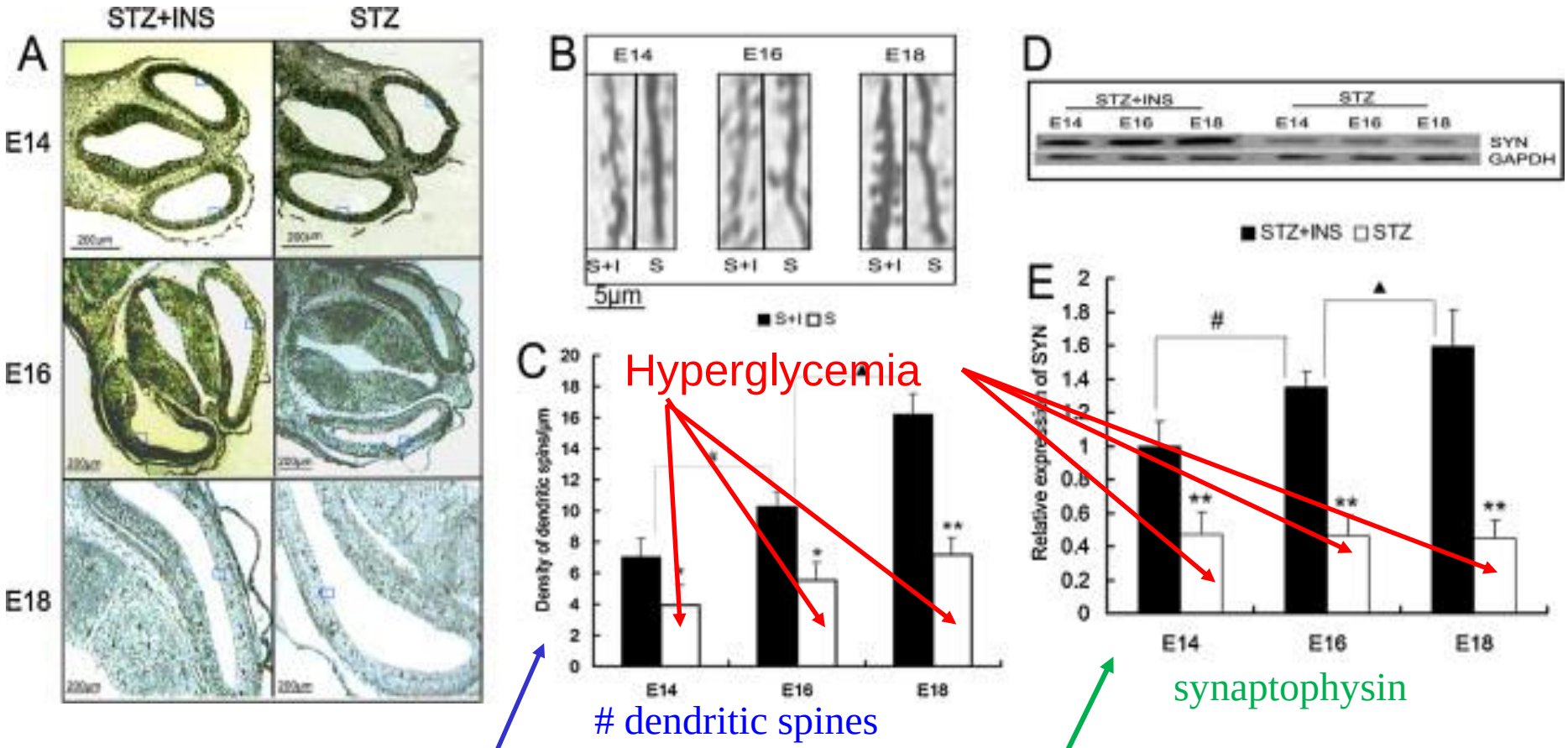
Hyperglycemia elicited negligible effects on brain formation but dramatic adverse effects on neural development.



Maternal hyperglycemia retarded dendritic development in the fetal subplate cortex. (A) Horizontal sections of fetal brain were stained by Golgi–Cox at E14, E16, and E18, squares indicate the location of dendritic spine evaluated. (B) Representative images of dendritic spine by Golgi–Cox staining. S + I, STS + Insulin; S, STZ. (C) The number of dendritic spines per μm was counted in five neurons from each section. (D) Representative images of WB to detect synaptophysin (SYN), a measure of synapse formation. The level of SYN expression was statistically reduced (E).

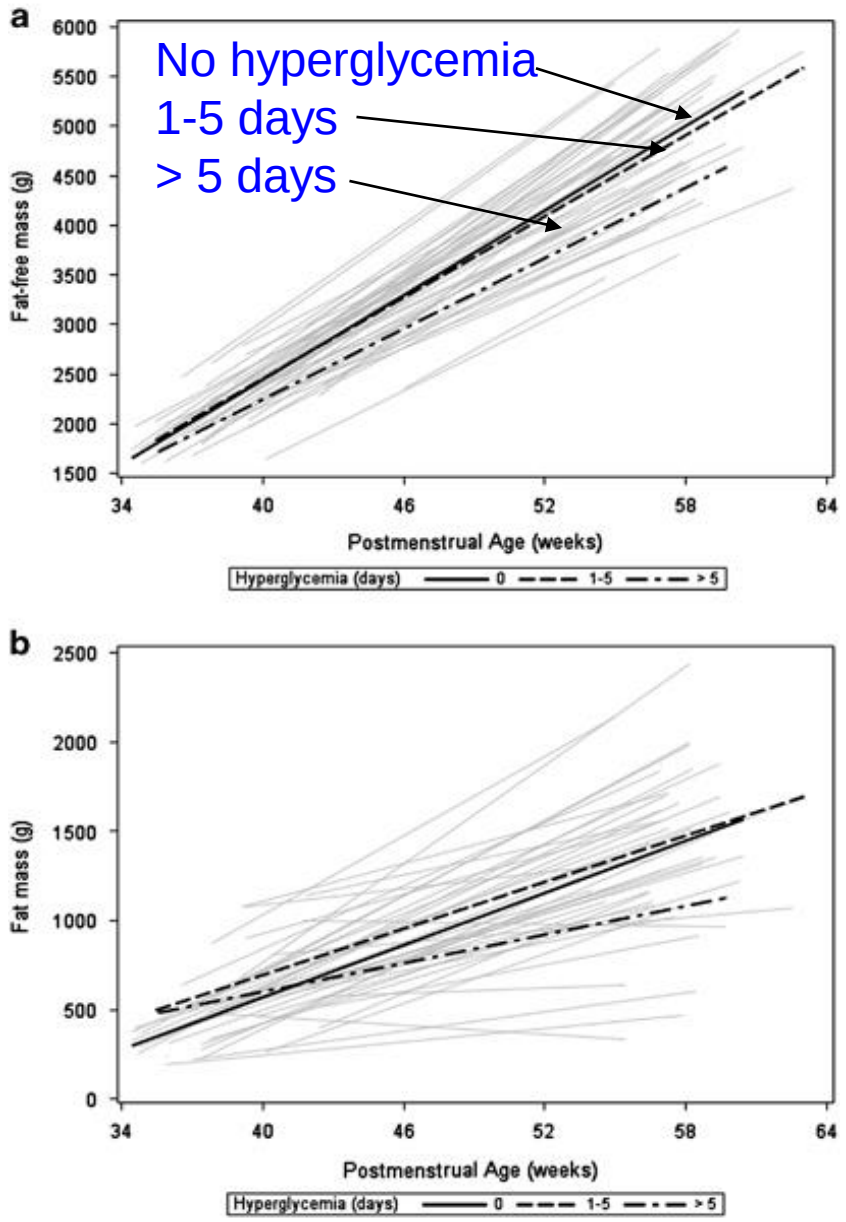
Jing Y-H, et al. Retardation of fetal dendritic development induced by gestational hyperglycemia is associated with brain insulin/IGF-I signals. International J Develop Neurosci 2014;37:15-20.

Rat pup study with subcutaneous Dextrose for 11 days

	Control	Moderate hyperglycemia	Severe hyperglycemia
Glucose, mg/dL	92	**344**	**427**
Wt, day 11, g	16.7	**13.8**	**11.2**
Death, n (%)	0	**2 (20)**	**4 (40)**
↓ **Neuronal Density**			
Dentate gyrus	94	**72**	**62**
Parietal cortex	50	**40**	**33**
(n/15,800 μm^2)			
↑ **Oxidant status**	5	**29**	**64**
↓ **Antioxidant Status**	9	**6**	**4**
(μmol H_2O_2 eq/g protein)			

Tayman C, et al. **Effects of Hyperglycemia on the Developing Brain in Newborns**. Pediatric Neurology 2014;51:239–245.

Even growth may be reduced with prolonged hyperglycemia.



Diminished growth and lower adiposity in hyperglycemic very low birth weight neonates at 4 months corrected age
Scheurer, JM, et al. (Ramel and Rao) J Perinatol 2016;**36:**145–150.

Postnatal body composition at discharge and 4 months CA of 44 VLBW AGA infants by days of hyperglycemia.
(a) Fat-free mass
(b) Fat mass.

Downregulation of the growth hormone axis may be responsible. These changes may influence long-term growth and cognitive development.

Early Enhanced Parenteral Nutrition, Hyperglycemia, and Death Among Extremely Low-Birth-Weight Infants

Table 2. Multivariable Logistic Regression Analysis for Death Given Survival at 12 Hours of Life Among 343 Infants

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Early enhanced parenteral nutrition[a]	1.59 (0.69-3.64)	.28
Gestational age	0.62 (0.49-0.79)	<.001
Clinical Risk Index for Babies	1.11 (1.01-1.23)	.03
Any vasopressor use	1.78 (0.89-3.55)	.10
Hyperglycemia during the first week of life[b]		
Mild	0.65 (0.16-2.66)	.55
Moderate	1.35 (0.43-4.32)	.61
Severe	4.68 (1.82-12.03)	.001

SI conversion factor: To convert glucose level to millimoles per liter, multiply by 0.0555.

[a] Born in 2006 to 2011 vs 2002 to 2005.

[b] Hyperglycemia was defined as 2 consecutive blood glucose levels in the defined range at least 3 hours apart and was categorized as mild (151-181 mg/dL), moderate (182-216 mg/dL), or severe (>216 mg/dL). Each infant was assigned only to the highest possible category. The reference category was not having mild, moderate, or severe hyperglycemia.

Table 3. Multivariable Logistic Regression Analysis for Death Given Survival at 7 Days of Life Among 319 Infants

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Early enhanced parenteral nutrition[a]	1.21 (0.41-3.54)	.73
Gestational age	0.52 (0.37-0.73)	<.001
Any vasopressor use	1.62 (0.70-3.76)	.26
Hyperglycemia during the first week of life[b]		
Mild	0.45 (0.05-4.31)	.49
Moderate	1.37 (0.27-7.02)	.71
Severe	8.63 (2.41-30.95)	<.001

SI conversion factor: To convert glucose level to millimoles per liter, multiply by 0.0555.

[a] Born in 2006 to 2011 vs 2002 to 2005.

[b] Hyperglycemia was defined as 2 consecutive blood glucose levels in the defined range at least 3 hours apart and was categorized as mild (151-181 mg/dL), moderate (182-216 mg/dL), or severe (>216 mg/dL). Each infant was assigned only to the highest possible category. The reference category was not having mild, moderate, or severe hyperglycemia.

Early Enhanced PN was not predictive of mortality, but severe hyperglycemia was predictive of mortality, independent of risk factors except gestational age.

Stensvold HJ, et al. JAMA Pediatr 2015;169:1003-1010.

Benefits of tight (insulin) glucose control?

Initial success, primarily noted in adult studies--

1. Reduced morbidity and mortality
2. Improved metabolic status (improved EE)
3. Improved cardiovascular status (CO)
4. Improved systemic and regional DO_2
5. Improved immunity, reduced infection, better wound healing, improved nitrogen balance.

But—highly controversial !

Subsequent trials (42 hospitals, 4 countries) failed to demonstrate benefits from tight glucose control and actually demonstrated significant excess mortality using the tight glucose range vs. the conventional range (did insulin make things worse?).

Thus, **Neonatal Hyperglycemia**

is common,

largely due to excess dextrose infusion
in the presence of stress responses,

and it is pathological and injurious.

How should it be prevented or treated?

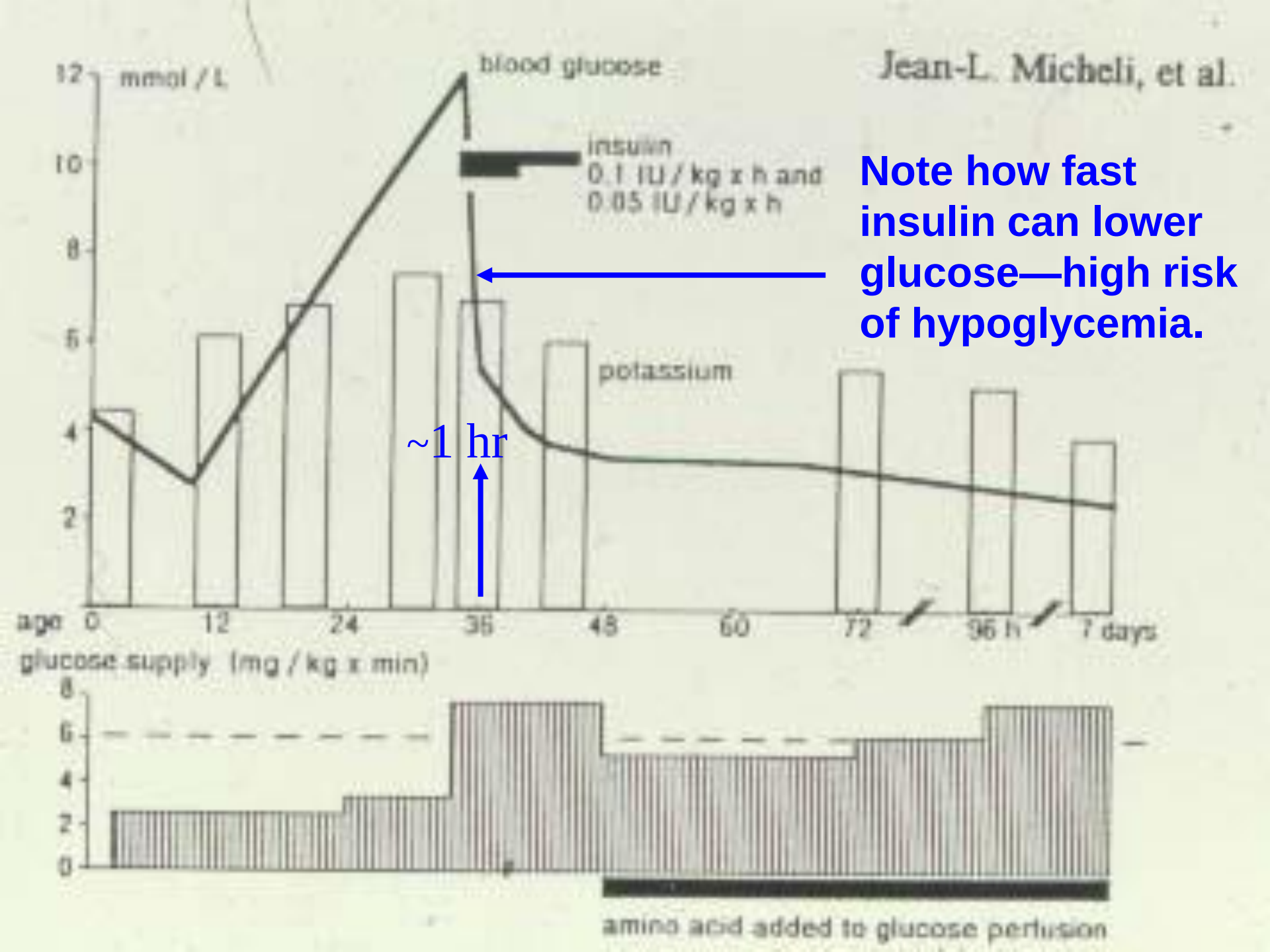
Prevention and Treatment of Hyperglycemia

1. **Start at lower IV dextrose infusion rates: 3-4 mg/kg/min**
2. **Earlier enteral feeding**
3. **Reduce IV dextrose infusion rate--!!**
   for example, first down to 8 mg/kg/min, then 6, then 4 --- even to 2 (but then would need gastric sterile water infusion to maintain total water intake).
4. **<u>Normalize physiology</u> with good medical care (reduces endogenous catecholamine and cortisol secretion).**
5. **<u>Reduce catecholamine</u> and <u>hydrocortisone</u> treatments.**
6. **<u>Reduce lipid</u> infusion (not shown to have a large immediate effect)**
7. **Increase IV amino acid infusion rate.**
8. **Advance enteral feeding.**

Increase insulin secretion

"Tight Glucose Control" in neonates using insulin to prevent (or treat) hyperglycemia: *Cautions! Limitations!*

- Insulin actually makes the baby fatter
- Insulin promotes fatty infiltration of heart and liver.
- Insulin increases complications of excess mitochondrial carbon load and ROS production.
- Insulin increases risk of hypoglycemia (Nirture Trial).
- Infused insulin does not promote glucose uptake or utilization by the brain or enhance neuronal growth or dendritic development.
- Insulin can lower plasma essential AA concentrations.
- Negative feedback mechanisms limit the effect of insulin to promote protein synthesis, net protein balance, and growth (*and might shorten leg length*—Auckland group)
- It just does not work as a growth hormone to augment growth when given in excess.



Note how fast insulin can lower glucose—high risk of hypoglycemia.

Insulin infusion
vs. reduced glucose infusion
to treat hyperglycemia
in 500-750 g infants

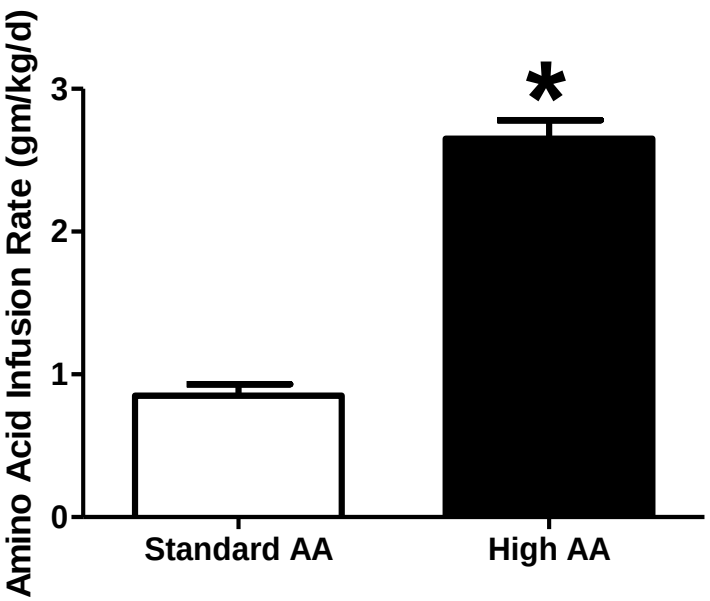
Bottino, Cowett , Sinclair, Cochrane Library, 2009, only one study to review—Meetze, et al. Biology of the Neonate 1998;74:214-21.

No difference in all age/weight groups on :

Death, Sepsis, ROP, NEC, ICH, CLD, NICU days, or Growth.

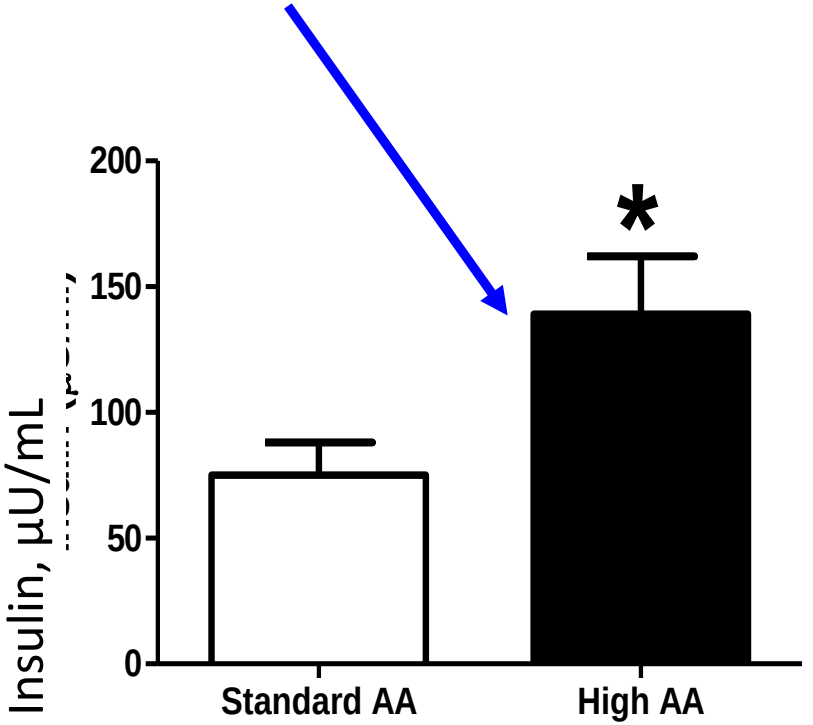
Perhaps safer, therefore, to just lower the glucose infusion rate.

And advance early parenteral nutrition with Amino Acids, which increase insulin secretion.



1 gm/kg/d 3 gm/kg/d

Goal Amino Acid Infusion Rate

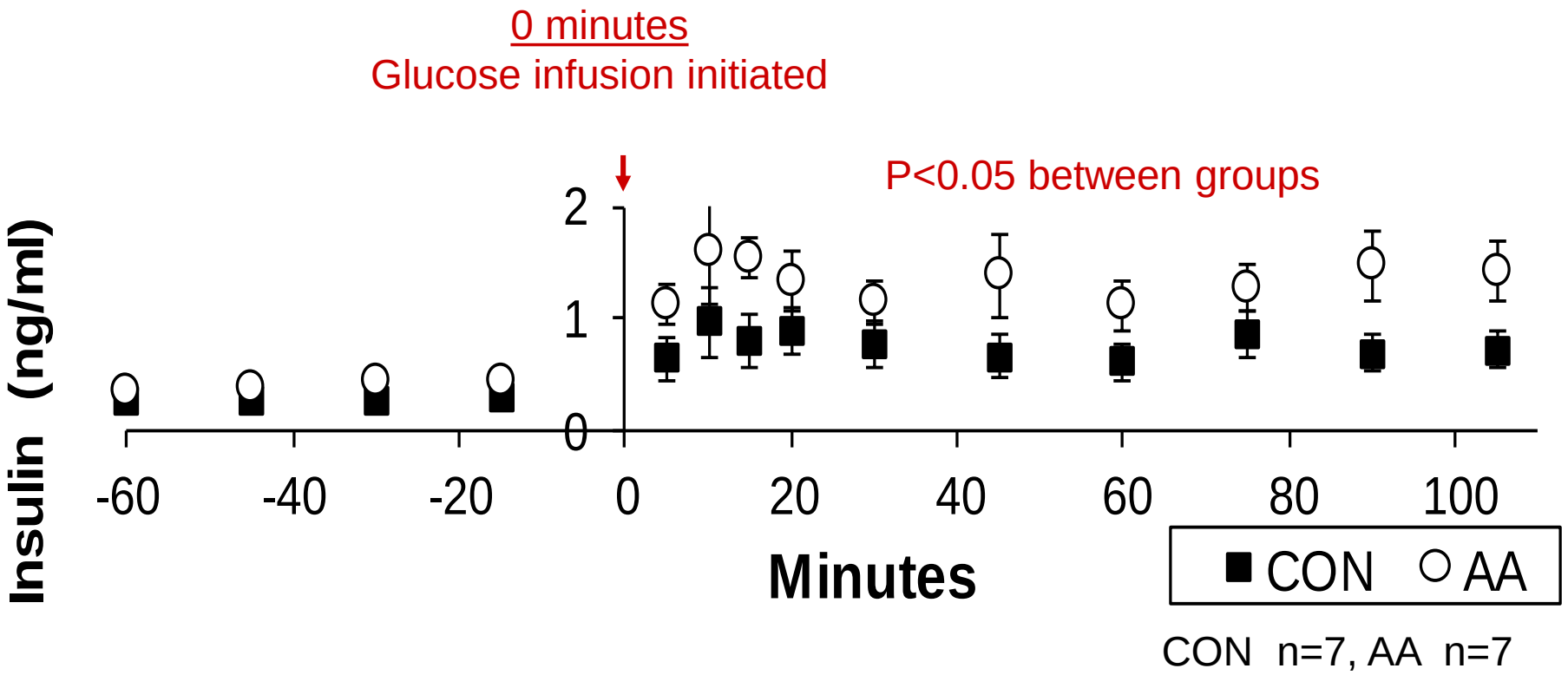


1 gm/kg/d 3 gm/kg/d

Goal Amino Acid Infusion Rate

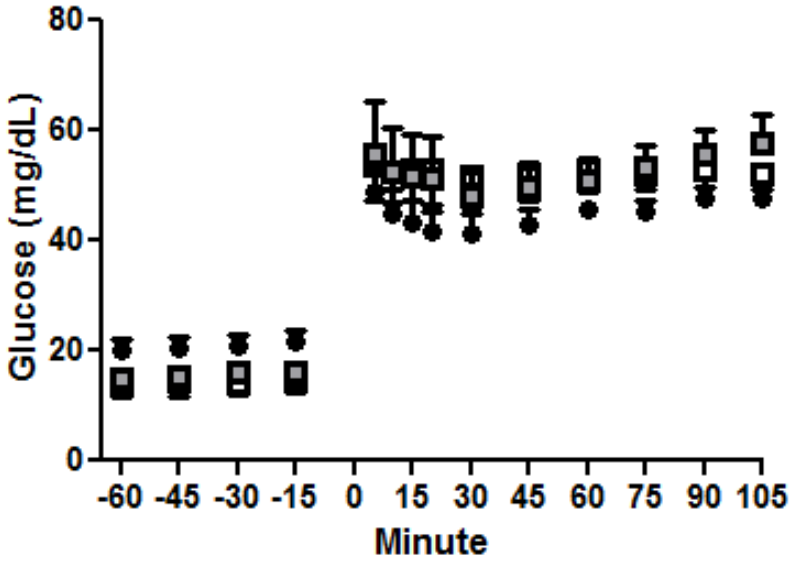
Thureen PJ, et al. Pediatr Res 2003;53:24-32.

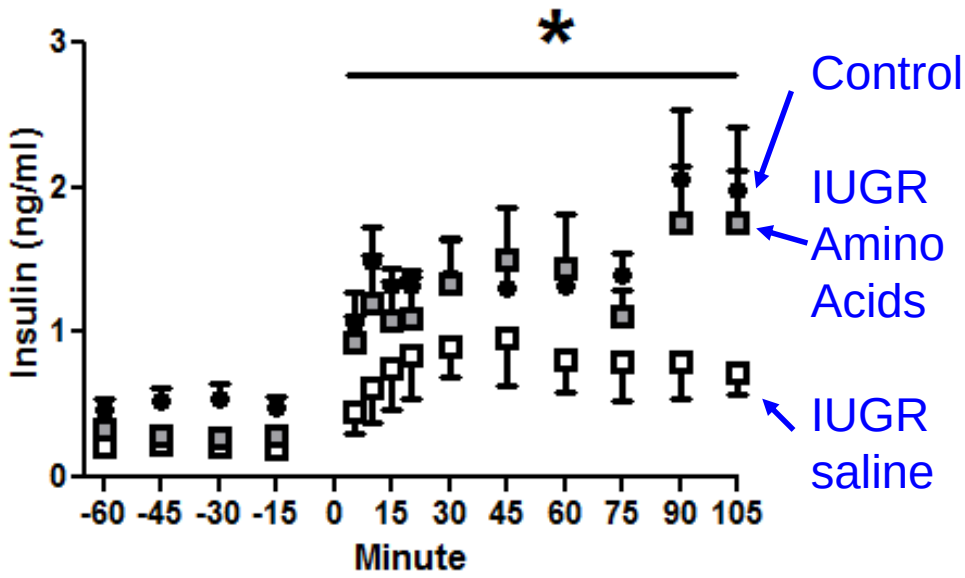
Amino Acid infusions in normal fetuses potentiate Glucose Stimulated Insulin Concentrations



Perhaps a better approach in preterm infants to promote insulin secretion?

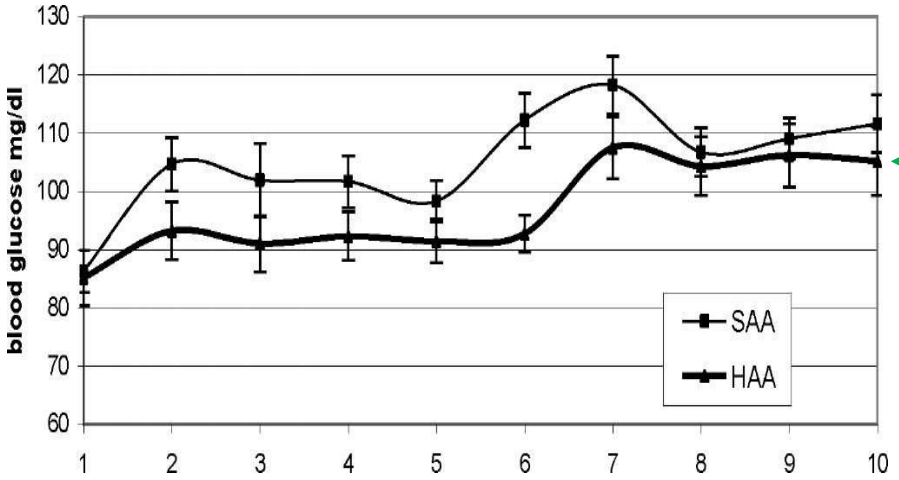
Increased amino acid supply also normalizes insulin secretion in IUGR fetuses





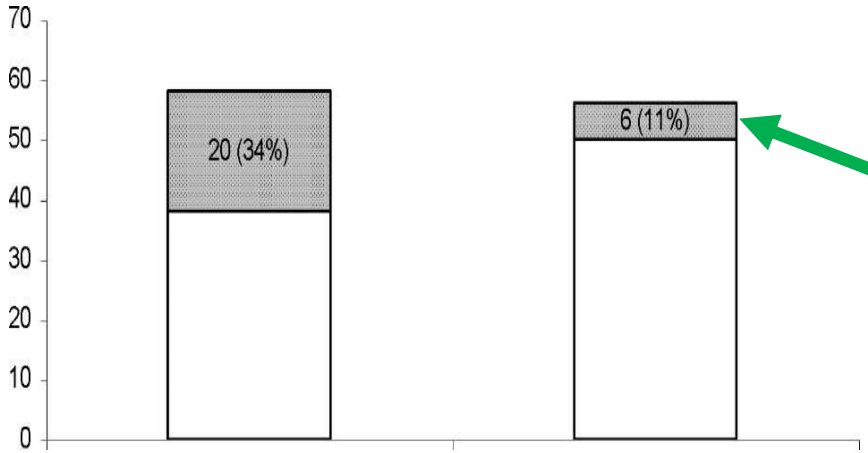
Perhaps a better approach in postnatal growth restricted preterm infants to promote insulin secretion, especially when produced by increased amino acid infusions to best promote protein accretion and muscle growth?

As a result, higher infusion rates of Amino Acids increase insulin production and promote glucose utilization.



Lower glucose concentrations

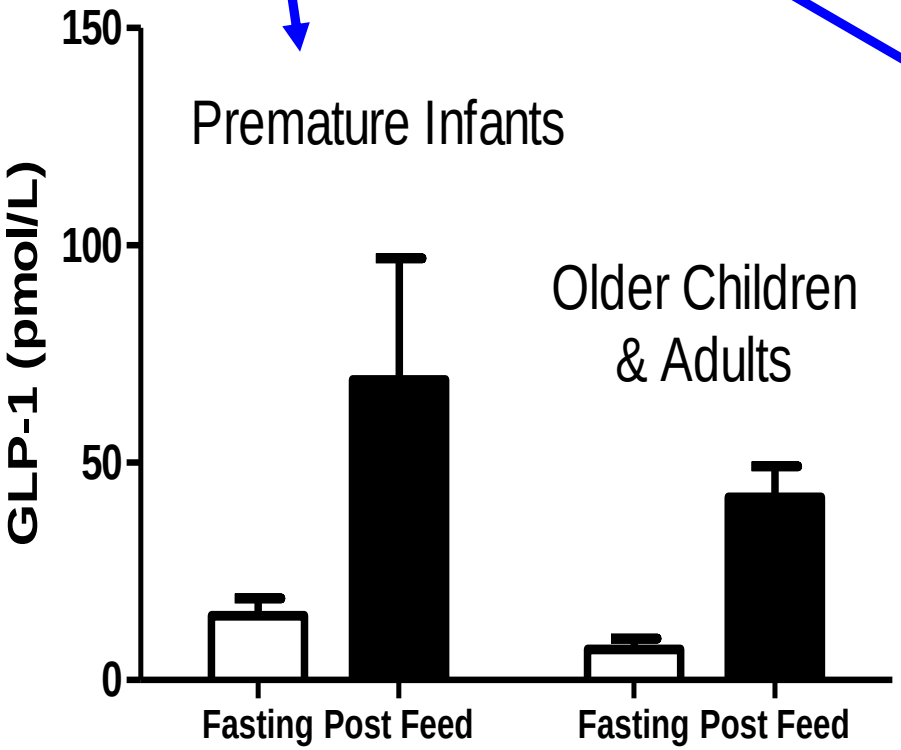
Longer-Term Higher AA Infusions, 4 g/kg/d vs. 2.5 g/kg/d of TrophAmine™.

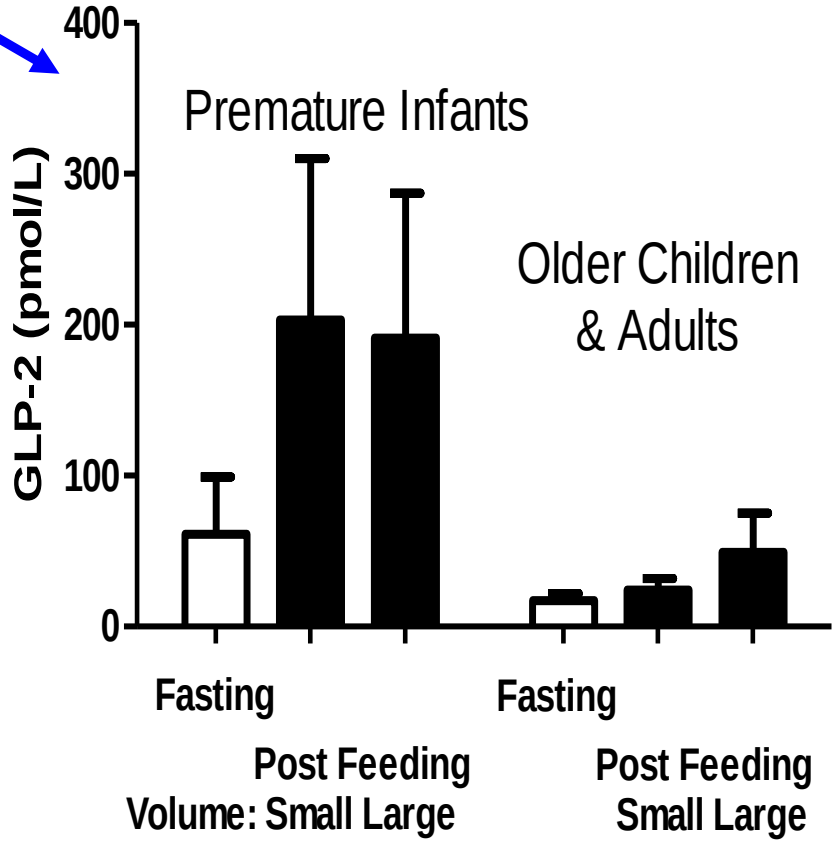


Less hyperglycemia

Burattini I, et al. *J Pediatrics*. 2013;163:1278-1282.
Bellagamba M, et al. J Pediatr Gastroenterol Nutr 2016; 62:879–884.

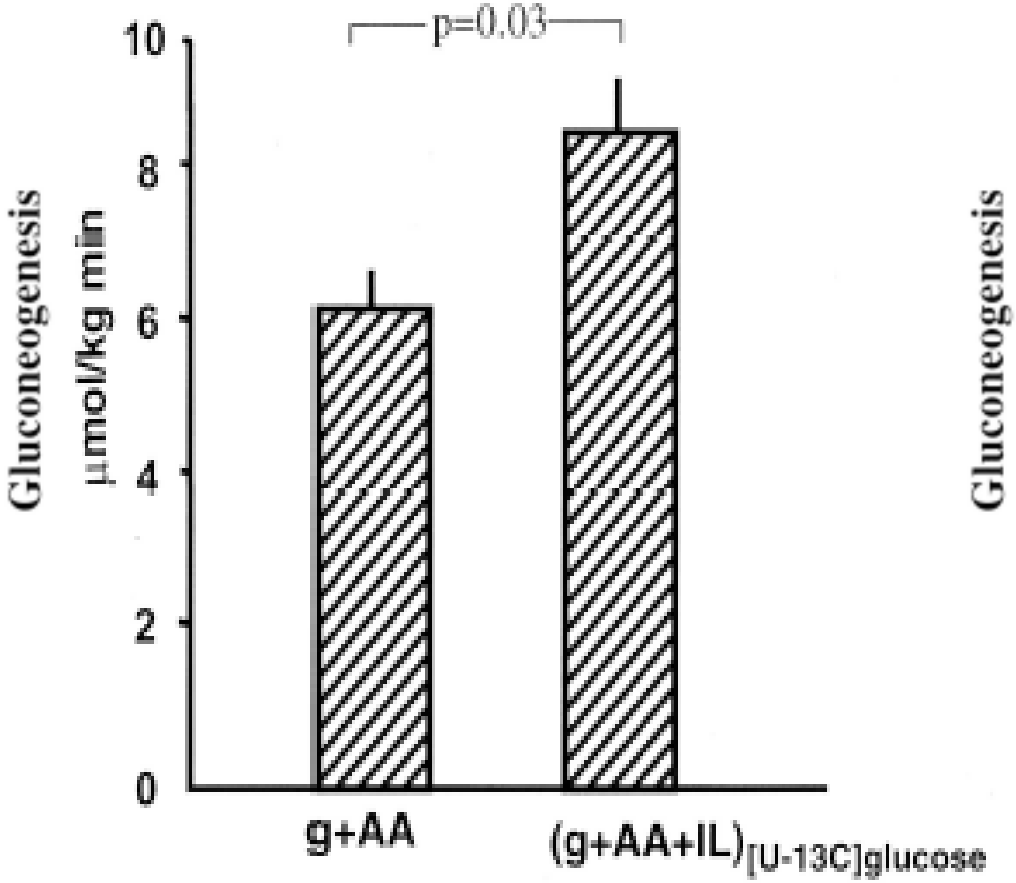
And use early enteral feeding, which increases incretins (GLP-1, GLP-2) that stimulate insulin secretion.

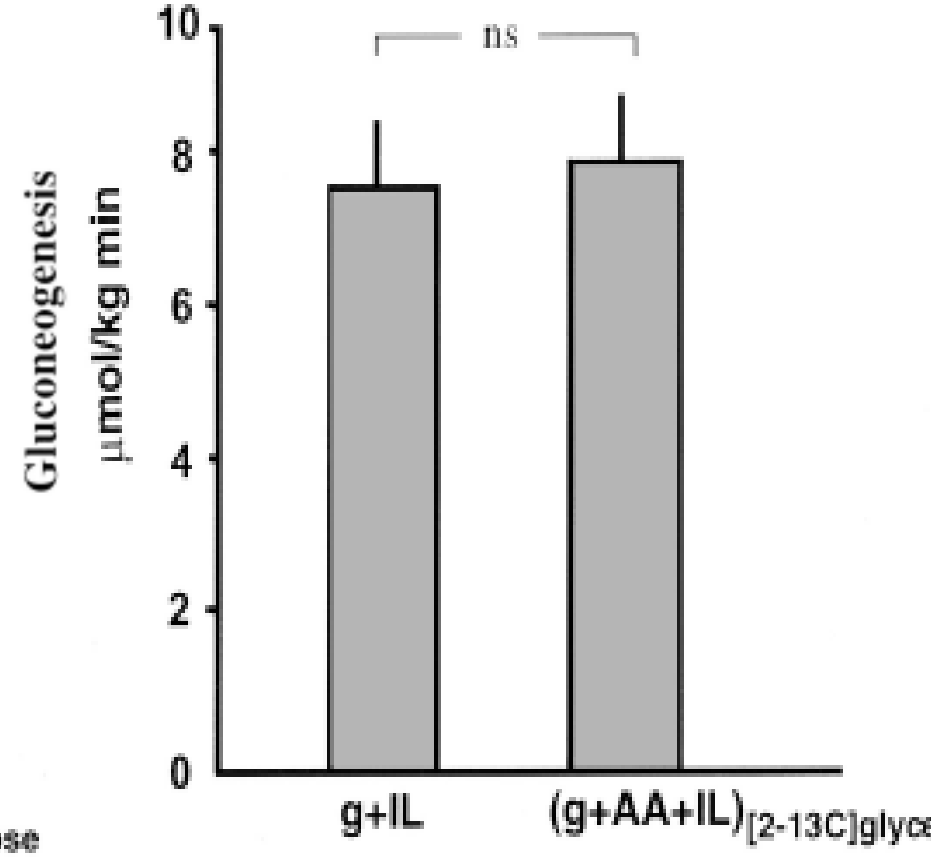




Amin H, et al. Pediatrics 2008;121:e180-e186.

Limit Intravenous Lipid Infusions During Hyperglycemia—reduced gluconeogenesis



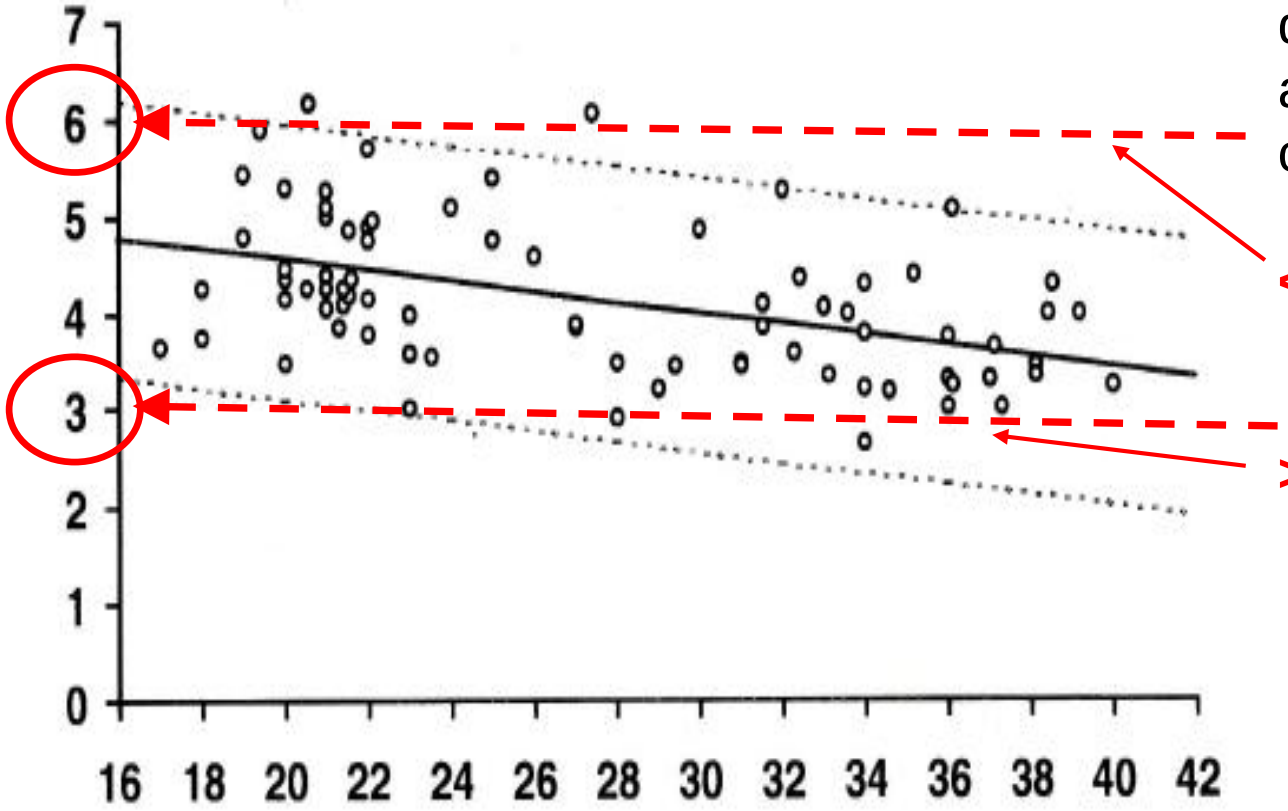


Sunehag, 2003

Given risks of sustained low and high glucose concentrations,

best to maintain plasma glucose concentrations in the normal range.

Plasma glucose concentrations in normal human fetuses.



Normal fetal development occurs at plasma glucose concentrations

<6 mM (<108 mg/dL),

>3 mM (>54 mg/dL).

Marconi AM, et al., Obstet Gynecol 1996;87:937-942.

University of Colorado Anschutz Medical Campus
School of Medicine

Thank you

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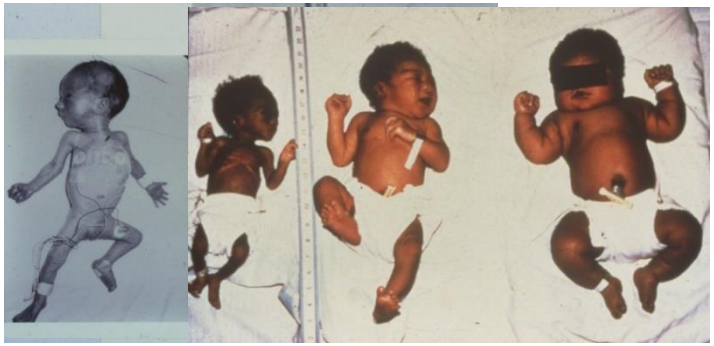

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