UNIVERSITY OF CAMBRIDGE
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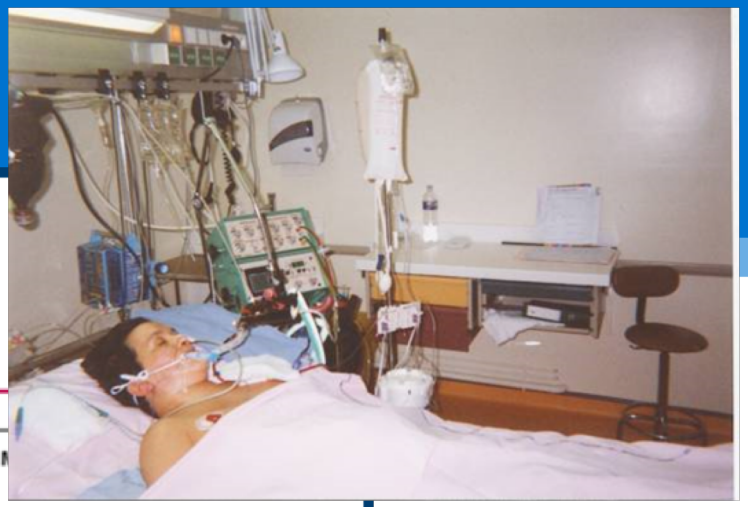
1209 - 2009

The Highs and Lows of Glucose Control in NICU

Physiology vs Pathology

Kathryn Beardsall kb274@cam.ac.uk

Department of Paediatrics

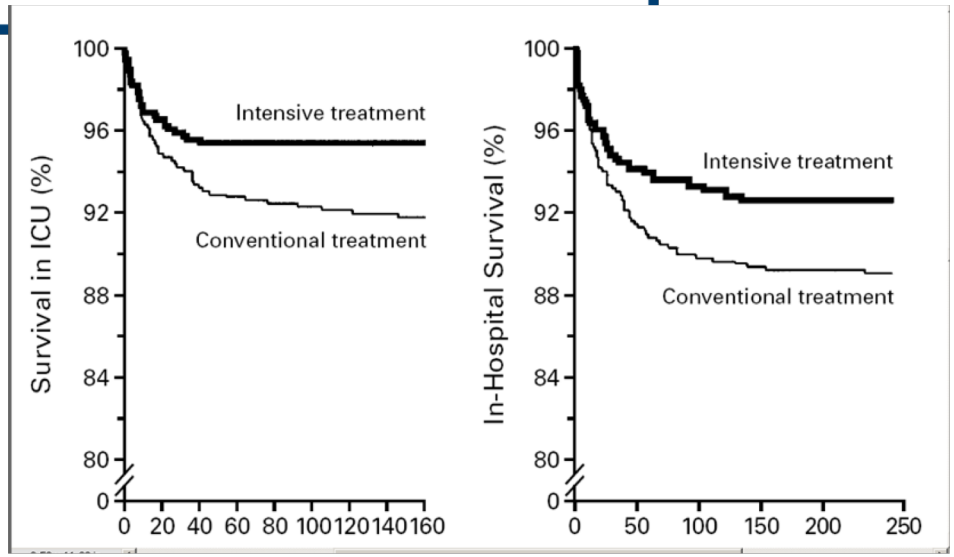


The New England Journal of Medicine

VOLUME 345 NOVEMBER 8, 2001 NU

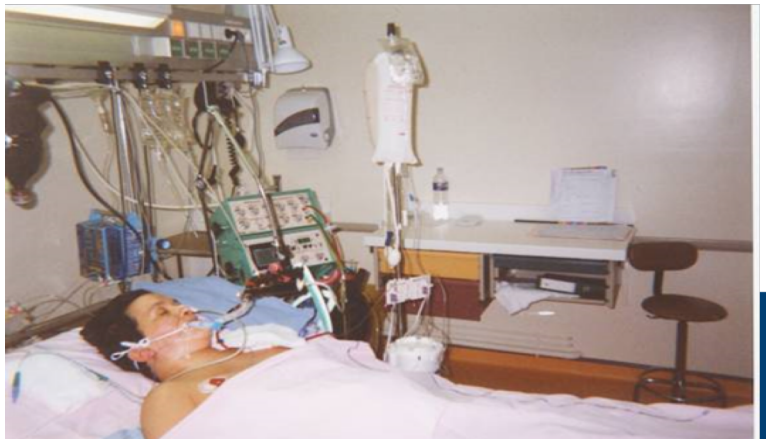
INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

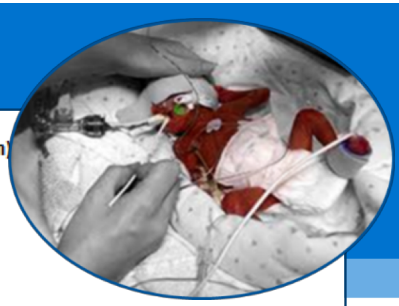


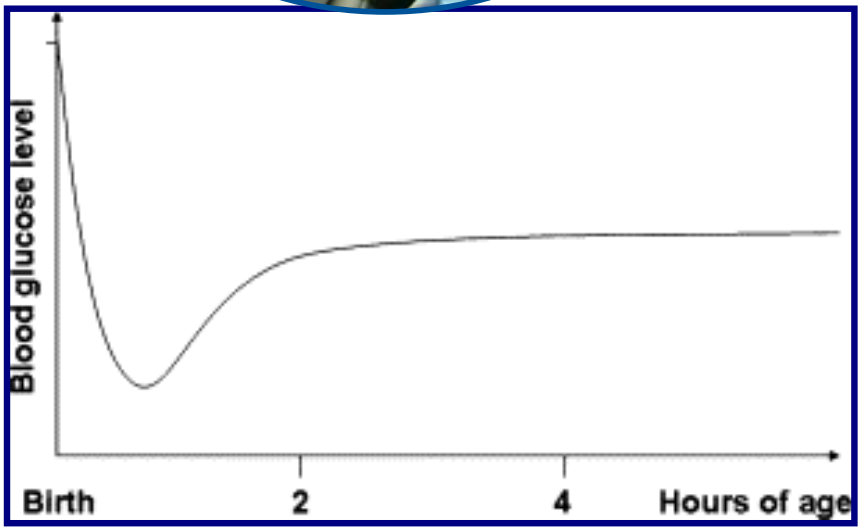
Neonatology – Transitioning

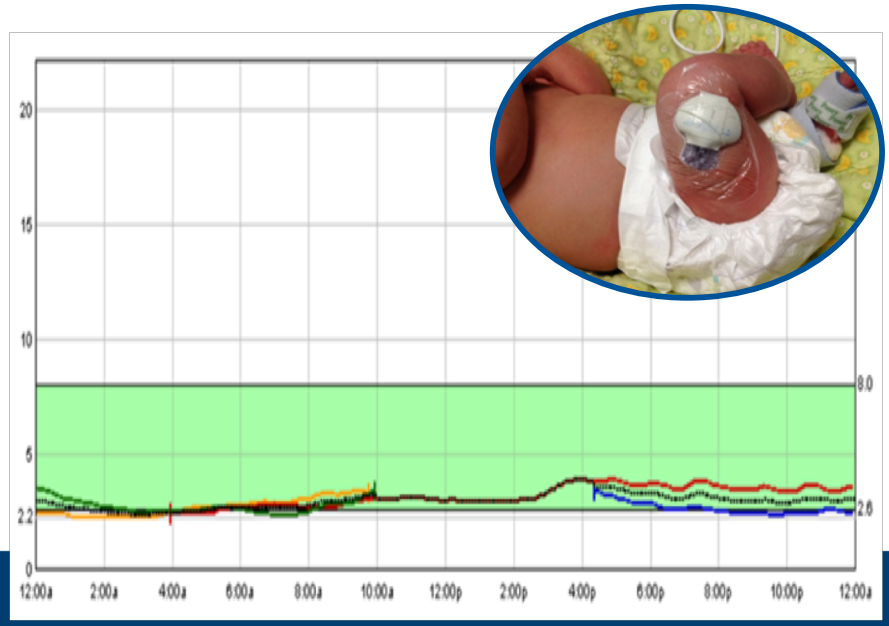
- Patients ‘well’ pathology is prematurity
- Nutrition is key to survival
- Metabolically critical period for adaptation



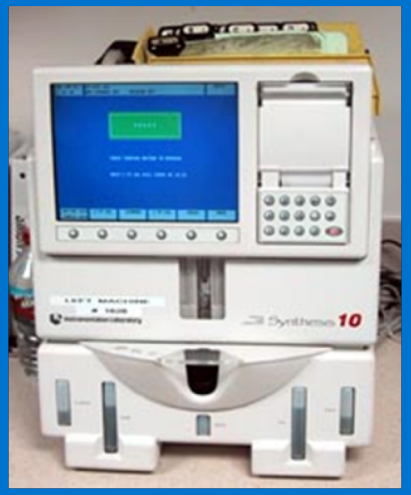
Metabolic Transition





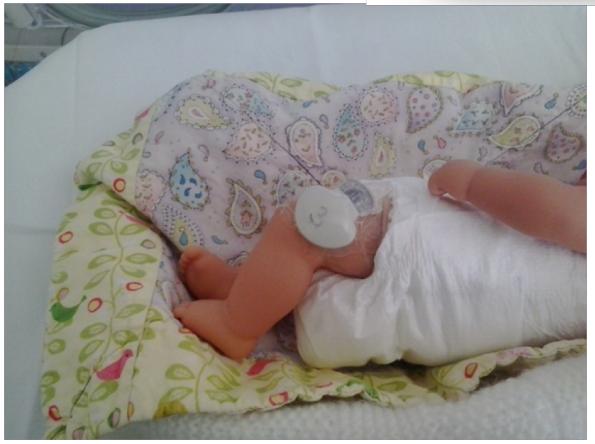


Glucose Measurement

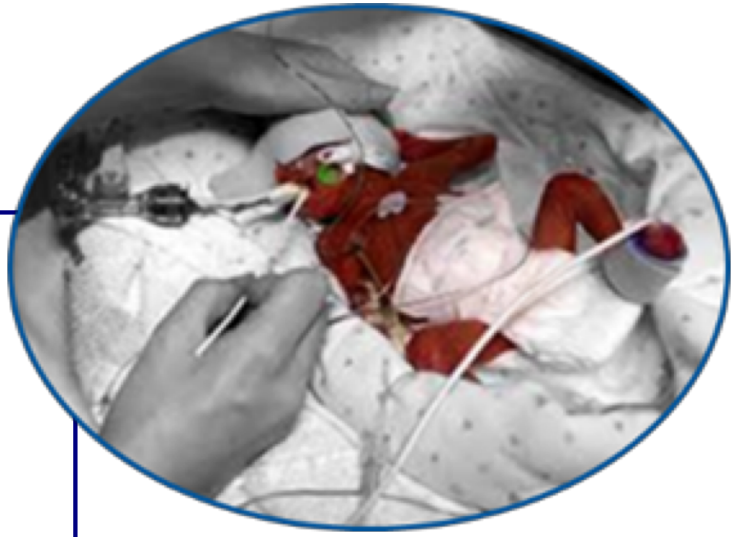


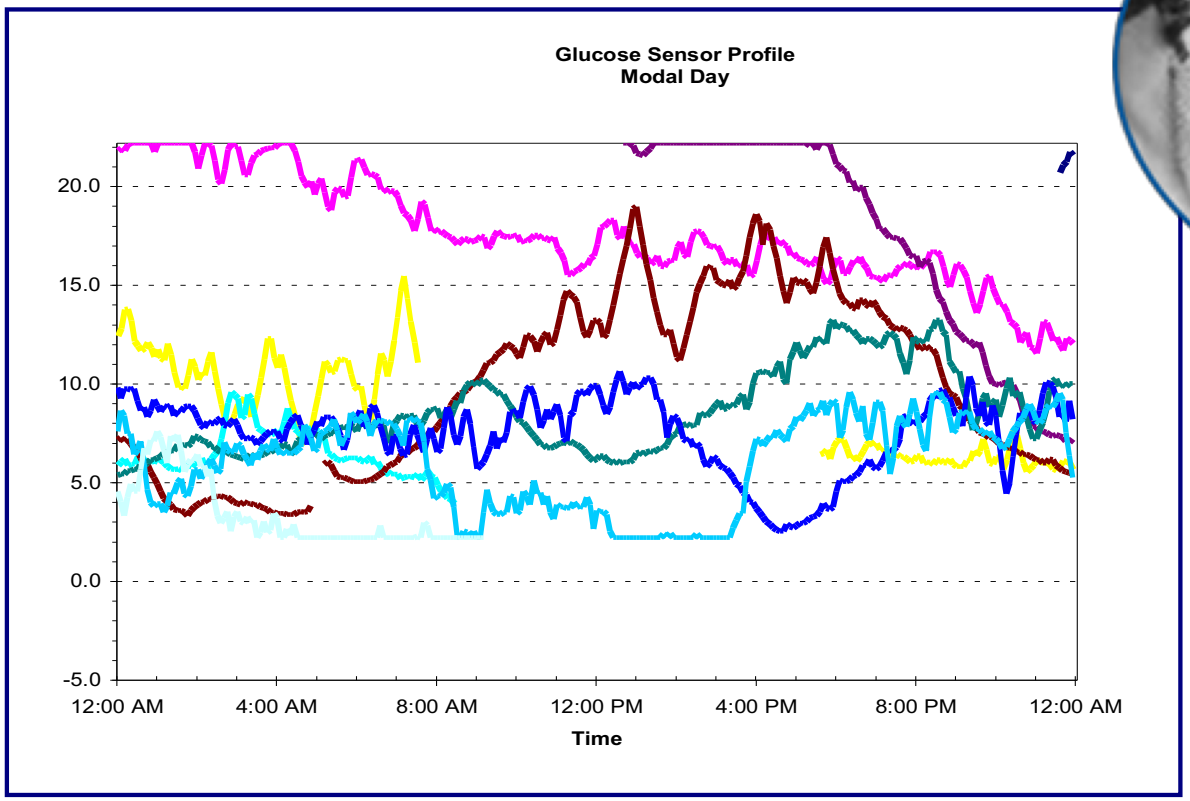
‘Optimising’ Glucose Control

Continuous Glucose Monitoring



Continuous Glucose Monitoring – preterm infant





Physiology vs Pathology

↑ Sympathetic outflow

↑ cytokines IL1, TNF

Sepsis

↑ catecholamines

Critical Illness

Limited alternative fuels

Prematurity

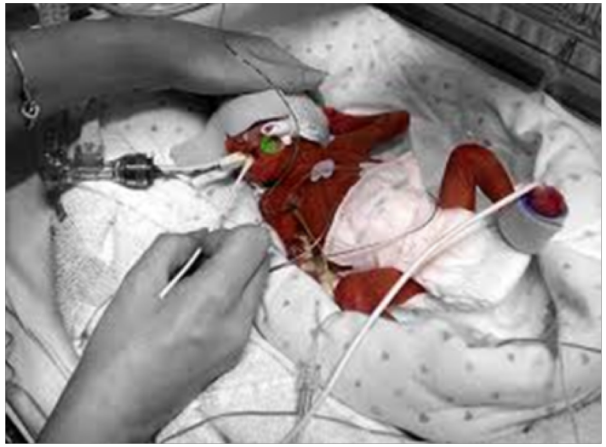
GLUT R

↑ proinsulin

↓ incretins

IUGR

↓ insulin



Acute Impact of Hyperglycaemia

- **Osmotic Diuresis** **Auerbach 2013**
  Fluid balance – intraventricular haemorrhage
  ?PDA

- **Oxidative Stress**
  Increase insulin independent glucose uptake by endothelial, hepatic, immune and nerve cells
  Increased free radical damage and mitochondrial dysfunction

- **Immune dysfunction**
  Impaired neutrophil function and phagocytic activity
  Glycosylation of Ig leads to altered complement fixation

- **Coagulation and fibrinolysis**
  Plasma FVIIa, FVIIC, FVIIIC, and TFPI

- **Pro-inflammatory**

Long term Impact - Mortality and Morbidity

- Death
- Intraventricular haemorrhage
- Bacterial Infection
- Fungal infection
- Retinopathy of prematurity
- NEC
- BPD
- Longer Hospital Stay
- Reduced white matter at term
- Growth

Rowen et al 1995

Garg et al 2003

Blanco et al 2006

Ertl et al 2006

Hays et al 2006

Kao et 2006

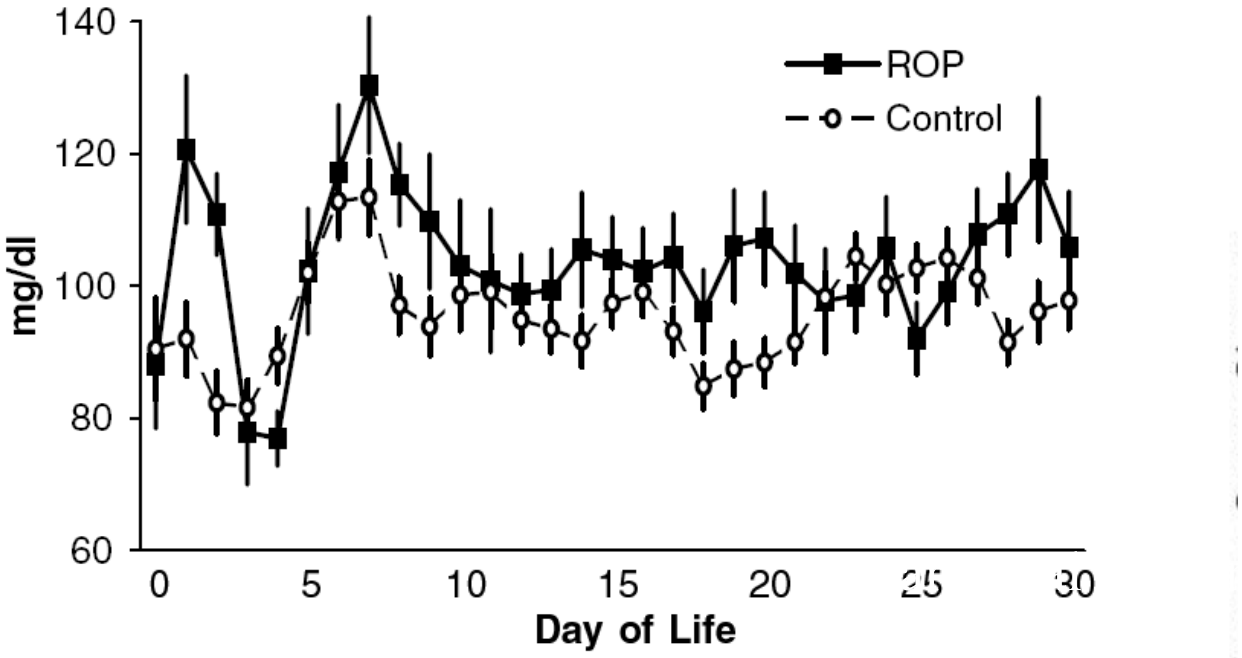
Manzoni et al 2006

Heilannet al 2007

Alexandrou 2011

Hyperglycaemia: links to morbidity

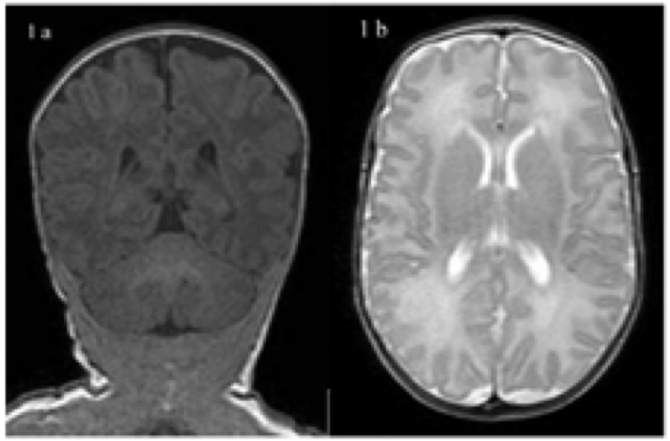
Increased risk of ROP for each 10 mg/dl increase of mean glucose (OR 2.7; 95% CI 1.003 to 7.27)



Garg 2003 J Perinatology

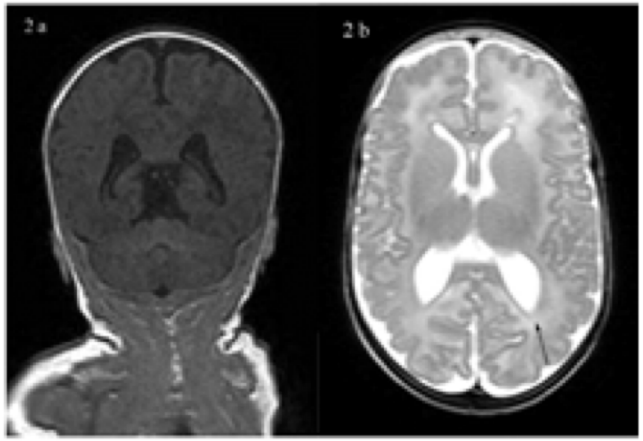
Early Hyperglycemia Is a Risk Factor for Death and White Matter Reduction in Preterm Infants

Normal white matter



T1-w. 3D FFE coronal (1a) and T2-w.TSE axial (1b) image scanned at term equivalent age showing normal white and gray matter, lateral ventricle size and appropriate gyration and myelination for GA in an eyglycemic infant.

Reduction in white matter volume



T1-w. 3D FFE coronal (2a) and T2-w. TSE axial (2b) image scanned at term equivalent age showing reduction in WM volume, most prominent occipital, dilated lateral ventricles, delayed gyral folding in a hyperglycemic infant.

Hyperglycaemic association with reduction in white matter
OR 3.1 [95% CI 1.0 –9.2] *P* .04).

Alexandrou Pedaitrics 2010

NIRTURE Hypothesis

Early intervention with continuous insulin replacement will prevent catabolism and improve glucose control, increase IGF-1 levels and could improve neonatal morbidity and mortality.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 30, 2008 VOL. 359 NO. 18

Early Insulin Therapy in Very-Low-Birth-Weight Infants

Kathryn Beardsall, M.R.C.P., Sophie Vanhaesebrouck, M.D., Amanda L. Ogilvy-Stuart, D.M., Christine Vanhole, Ph.D., Christopher R. Palmer, Ph.D., Mirjam van Weissenbruch, Ph.D., Paula Midgley, M.D., Michael Thompson, F.R.C.P., Marta Thio, M.D., Luc Cornette, M.D., Iviano Ossuetta, M.R.C.P., Isabel Iglesias, M.D., Claire Theyskens, M.D., Miranda de Jong, M.D., Jag S. Ahluwalia, F.R.C.P.C.H., Francis de Zegher, Ph.D., and David B. Dunger, M.D.

? Hyperglycaemia vs hypoglycaemia

? Poor nutritional intake

Tight Glycemic Control With Insulin in Hyperglycemic Preterm Babies: A Randomized Controlled Trial

AUTHORS: Jane M. Alsweiler, MBChB, FRACP, PhD,[a,b] Jane E. Harding, MBChB, DPhil, FRACP,[b] and Frank H. Bloomfield, MBChB, FRACP, PhD[a,b]

[a]*Department of Paediatrics: Child and Youth Health and* [b]*Liggins Institute, University of Auckland, Auckland, New Zealand*

WHAT'S KNOWN ON THIS SUBJECT: Insulin is commonly used to treat neonatal hyperglycemia, but there are few data to support its use. Tight glycemic control with insulin improves outcome in diabetic patients, but it is not known whether it is effective in hyperglycemic preterm infants.

Single centre n=88 babies

<30/40 <1500g

Tight 4-6mmol/l
Control 8-10mmol/l

Hyperglycemia > 2 BG > 8.5mmol/l

Results

Mean BG	5.7 (4,8-6.7) mmol/l	vs	6.5 (5.1-8.2) mmol/l
Hypoglycaemia	25/43 (58%)	vs	12/45 (27%)

REACT

Real Time Continuous Glucose Monitoring in Neonatal Intensive Care

NHS
National Institute for Health Research

Objectives

- To evaluate the ***efficacy*** of rCGM in helping control levels of glucose in the preterm infant
- To evaluate clinical ***acceptability*** in the preterm infant
- To assess ***safety*** in terms of risk for hypoglycaemia in the preterm infant
- To evaluate the ***cost-effectiveness*** and NHS importance of such an intervention

Trial Eligibility

Inclusion Criteria

- Parental informed consent
- ≤ 33+6 weeks gestation
- ≤ 24 hours of age
- Birth weight ≤1200g

Exclusion Criteria

- A lethal congenital abnormality known at trial entry
- Any congenital metabolic disorder known at trial entry
- Neonates who, in the opinion of the treating clinician at trial entry, have no realistic prospect of survival

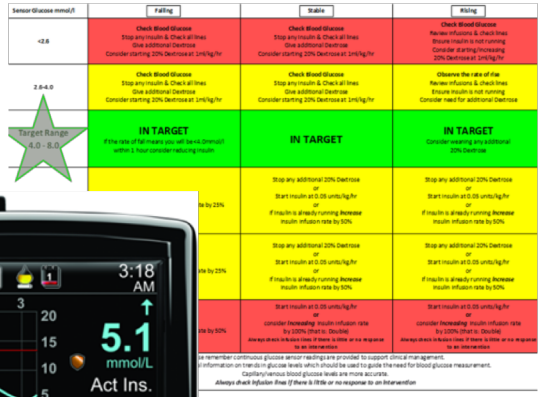
Trial Intervention

Intervention

MiniMed 640G

Real time CGMs

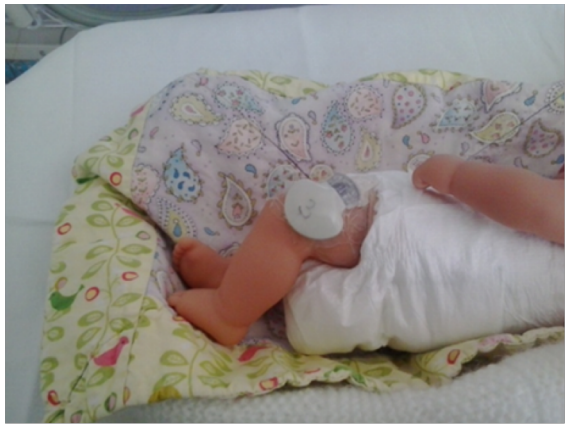
+ paper based algorithm



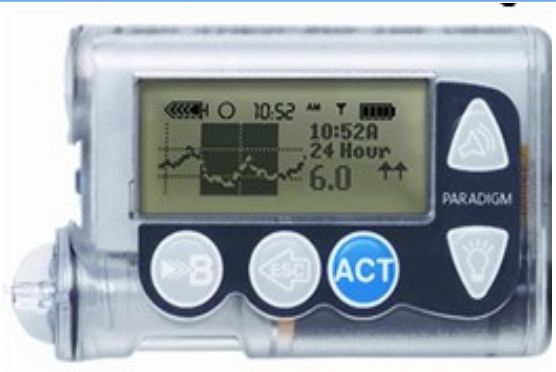
Control

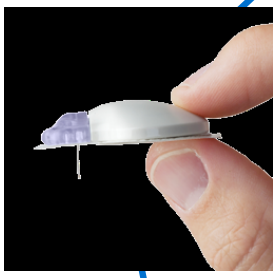
Standard clinical management

+ blinded CGMs data capture



CGM with Paper Algorithm

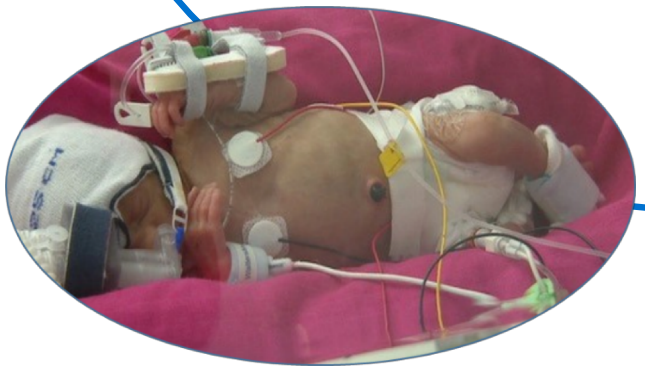




Target SG 4.0-8.0 mmol/l

(72-144mg/dl)

D1-7



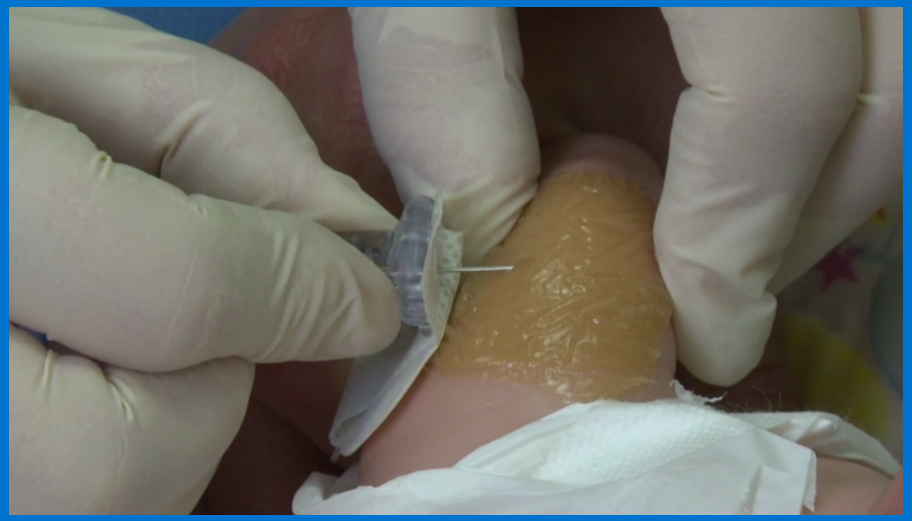
Sensor Glucose mmol/l	Falling	Stable	Rising
<2.6	**Check Blood Glucose** Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Review infusions & check lines Ensure insulin is not running Consider starting/increasing 20% Dextrose at 1ml/kg/hr
2.6-4.0	**Check Blood Glucose** Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Check Blood Glucose** Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	**Observe the rate of rise** Review infusions & check lines Ensure insulin is not running Consider need for additional Dextrose
Target Range 4.0 - 8.0	**IN TARGET** If the rate of fall means you will be <4.0mmol/l within 1 hour consider reducing insulin	**IN TARGET**	**IN TARGET** Consider weaning any additional 20% Dextrose
8.0-10.0	**Observe the rate of fall** Consider ***reducing*** insulin infusion rate by 25%	Stop any additional 20% Dextrose or Start insulin at 0.05 units/kg/hr or If insulin is already running ***increase*** insulin infusion rate by 50%	Stop any additional 20% Dextrose or Start insulin at 0.05 units/kg/hr or If insulin is already running ***increase*** insulin infusion rate by 50%
10-15.0	**Observe the rate of fall** Consider ***increasing*** insulin infusion rate by 25%	Stop any additional 20% Dextrose or Start insulin at 0.05 units/kg/hr or If insulin is already running ***increase*** insulin infusion rate by 50%	Stop any additional 20% Dextrose or Start insulin at 0.05 units/kg/hr or If insulin is already running ***increase*** insulin infusion rate by 50%
>15	**Observe the rate of fall** Consider ***increasing*** insulin infusion rate by 50%	Start insulin at 0.05 units/kg/hr or consider ***increasing*** insulin infusion rate by 100% (that is: Double) Always check infusion lines if there is little or no response to an intervention	Start insulin at 0.05 units/kg/hr or consider ***increasing*** insulin infusion rate by 100% (that is: Double) Always check infusion lines if there is little or no response to an intervention
CRITICAL CONCERN IN TARGET	Please remember continuous glucose sensor readings are provided to support clinical management. They provide additional information on trends in glucose levels which should be used to guide the need for blood glucose measurement. Capillary/venous blood glucose levels are more accurate. ***Always check infusion lines if there is little or no response to an intervention***		

The Sensor

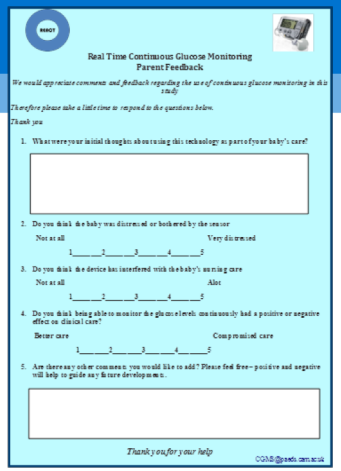
Standard Insertion

ion

Neonatal Insertion



Outcomes



Real Time Continuous Glucose Monitoring
Parent Feedback

We would appreciate comments and feedback regarding the use of continuous glucose monitoring in this study

Therefore please take a little time to respond to the questions below.

Thank you

1. What were your initial thoughts about using this technology as part of your baby's care?
2. Do you think the baby was distressed or bothered by the sensor
   Not at all ____1____2____3____4____5 Very distressed
3. Do you think the device has interfered with the baby's nursing care
   Not at all ____1____2____3____4____5 Alot
4. Do you think being able to monitor the glucose levels continuously had a positive or negative effect on clinical care?
   Better care ____1____2____3____4____5 Compromised care
5. Are there any other comments you would like to add? Please feel free – positive and negative will help to guide any future developments.

Thank you for your help

CGMS@leeds.ac.uk

Efficacy

Time in Target SG 2.6-10mmol/l
Mean SG in first 6 days.
Time in Target SG 4-8mmol/l
SG variability
Time hyperglycaemic- SG >15mmol/l

Acceptability

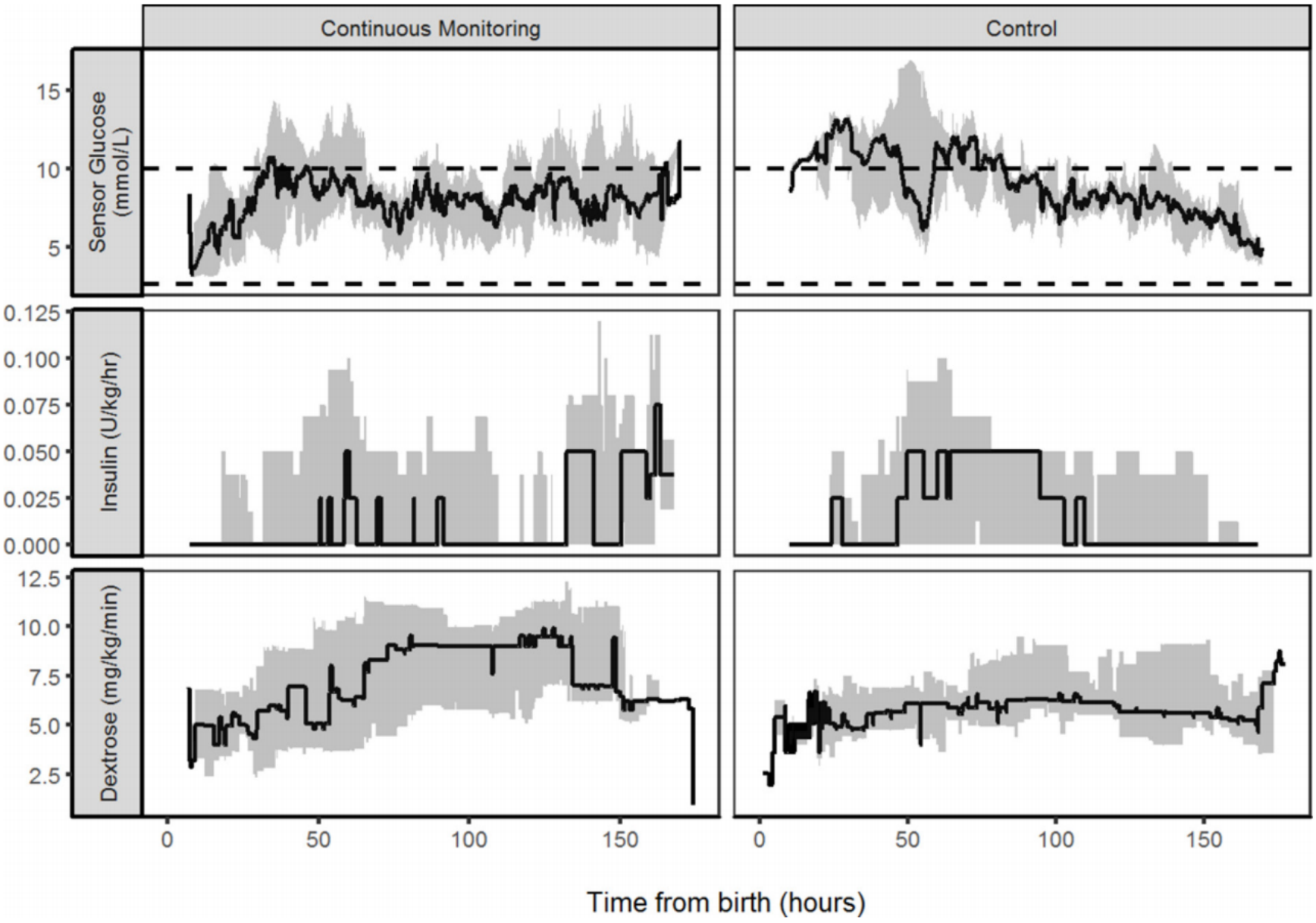
Clinical staff rating score of impact on clinical care
Frequency of blood glucose monitoring

ADVERSE EVENT		
Did any adverse event occur after the last visit?—*Indicator Question*		Yes ☐ 1 No ☐ 2
If "Yes", please provide the information in the adverse events (AE) page (page no. XX) and give details below:–Skip		
AE page number	AE serial number	Did any unscheduled visit happen after the last visit? *(Please provide details on page no. YY)–Skip*
☐☐	☐☐	Yes ☐ 1 No ☐ 2
☐☐	☐☐	Yes ☐ 1 No ☐ 2
☐☐	☐☐	Yes ☐ 1 No ☐ 2

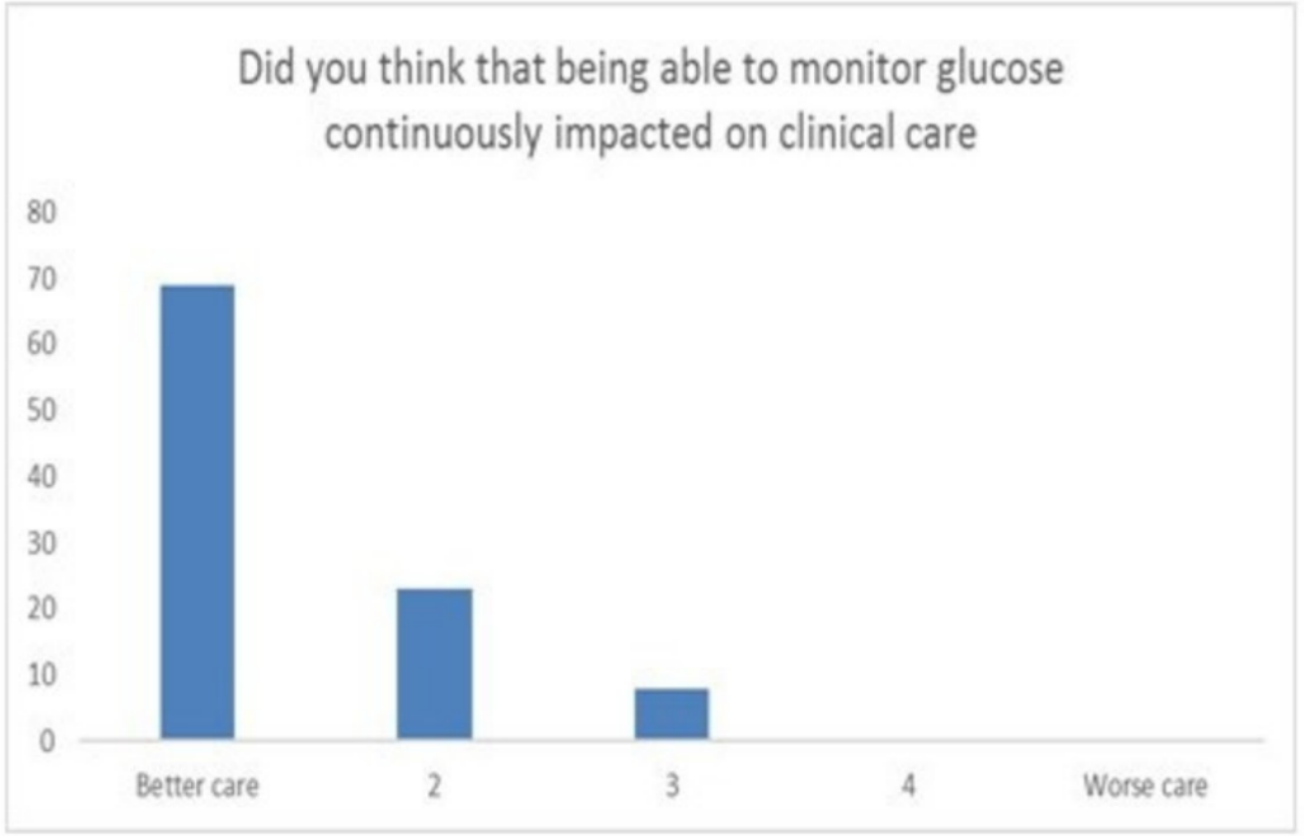
Safety

Incidence of hypoglycaemia BG >2.2mmol/l and <2.6mmol/l
Incidence of hypoglycaemia SG <2.6mmol/l for >1hour
Incidence of severe hypoglycaemia any episode of BG ≤2.2mmol/l

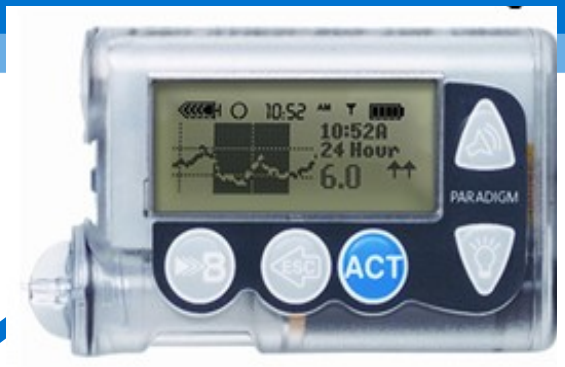
Health Economics

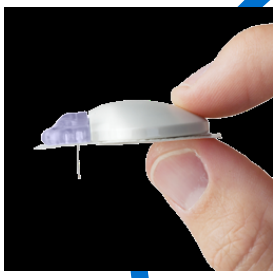

Continuous Monitoring
Control
Sensor Glucose (mmol/L)
15
10
5
Insulin (U/kg/hr)
0.125
0.100
0.075
0.050
0.025
0.000
Dextrose (mg/kg/min)
12.5
10.0
7.5
5.0
2.5
0
50
100
150
Time from birth (hours)

Staff Perspective



Challenges in NICU





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2.6-4.0	Check Blood Glucose Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	Check Blood Glucose Stop any insulin & Check all lines Give additional Dextrose Consider starting 20% Dextrose at 1ml/kg/hr	Observe the rate of rise Review infusions & check lines Ensure insulin is not running Consider need for additional Dextrose
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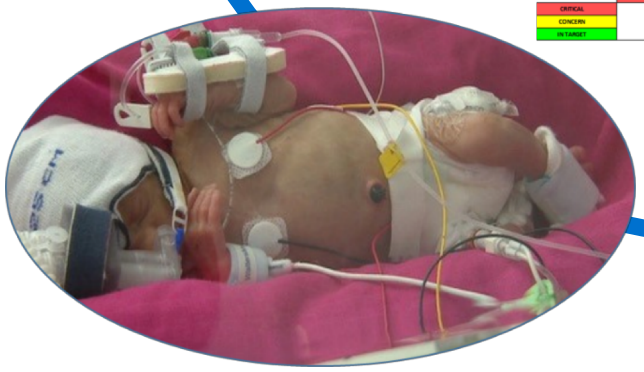
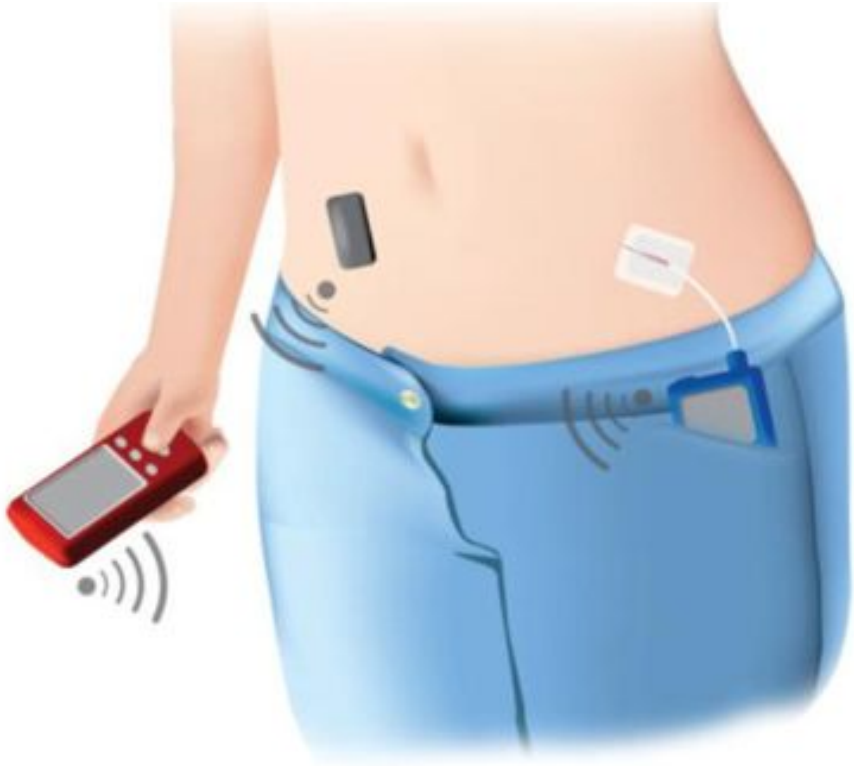
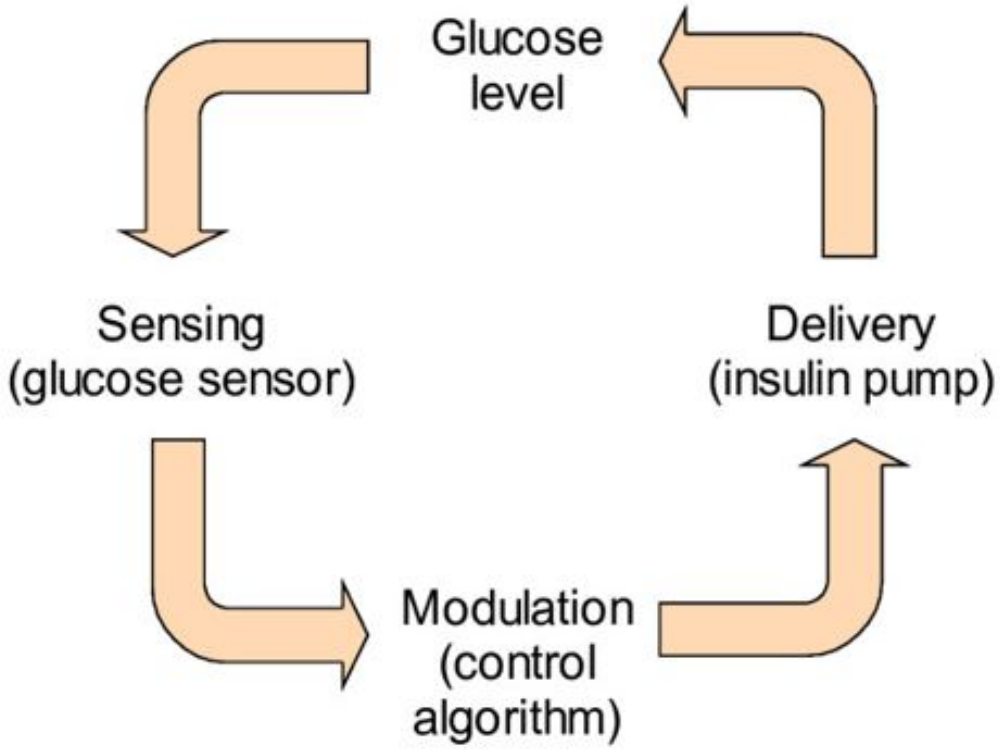
CRITICAL	Please remember continuous glucose sensor readings are provided to support clinical management.		
CONCERN	They provide additional information on trends in glucose levels which should be used to guide the need for blood glucose measurement.		
IN TARGET	Capillary/venous blood glucose levels are more accurate.		
	Always check infusion lines if there is little or no response to an intervention		



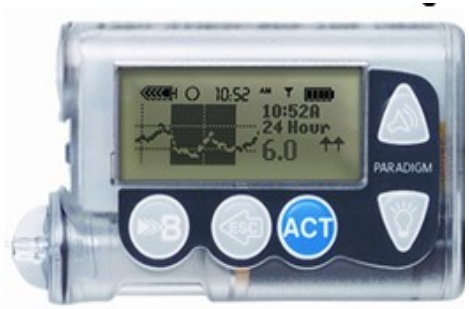
- Wealth of Data
- Complex patients
  - Individual
  - Multiple infusions
- Staffing
  - High intensity
- Risk
  - Hypoglycaemia

Closing the Loop with CGM

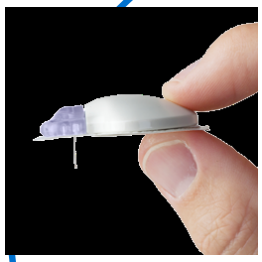




Closing the Loop with CGM



48-72 hours

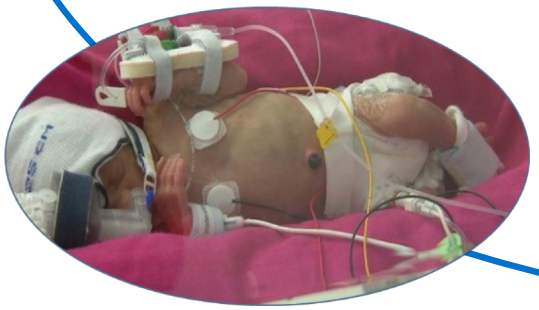


Optimised *in silico*

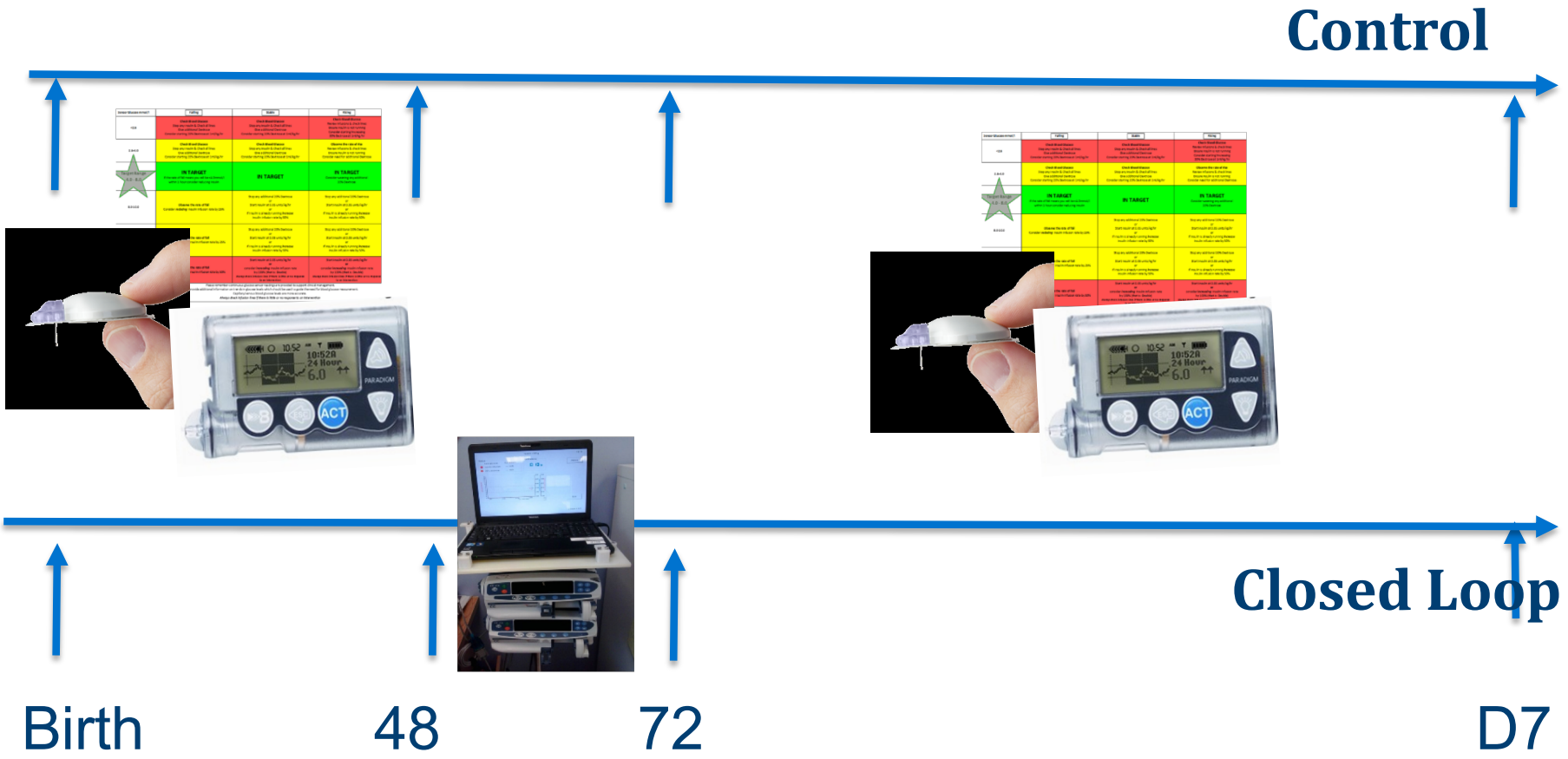
SG values every 15 minutes

Advice on insulin infusion rates

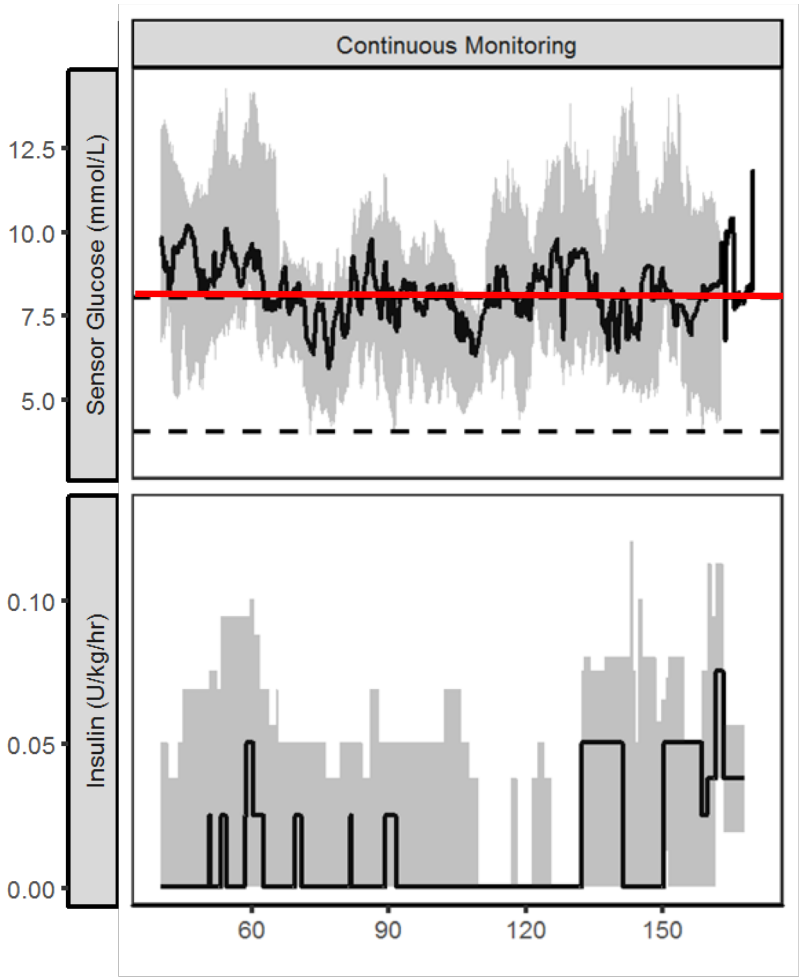
Adapts to each baby

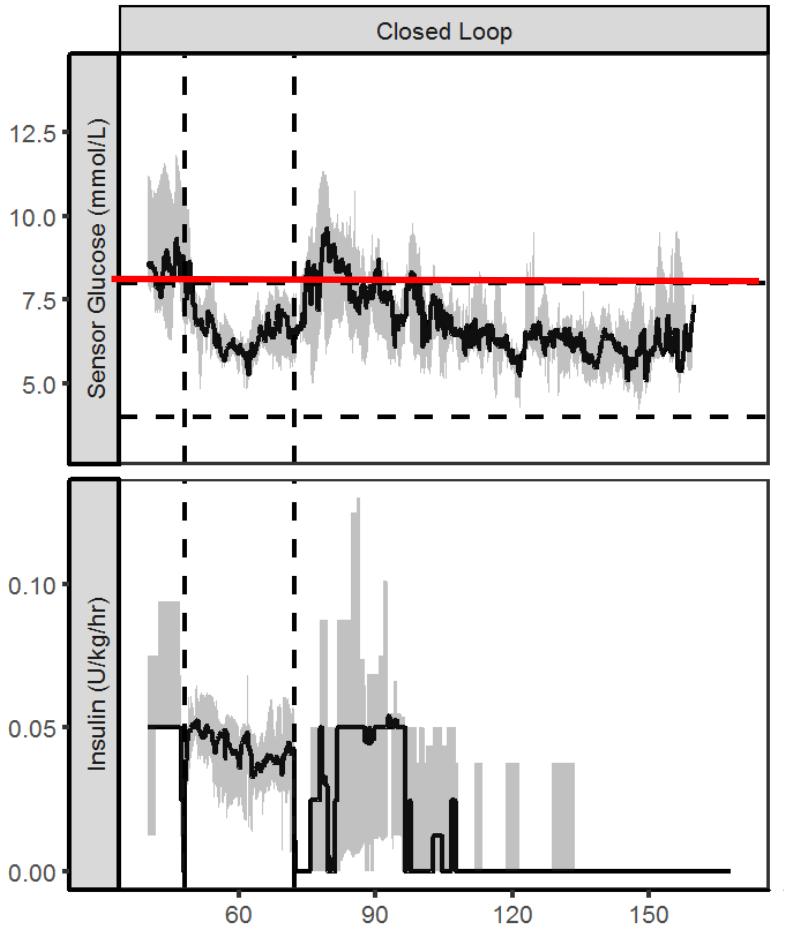


Intervention



Closing the Loop





Results 48-72 hours

	Closed-loop (n=10)	Control (n=10)
Time spent with sensor glucose level (%)		
4.0 to 8.0 mmol/l[a]	91 (78, 99)	26 (6, 64)
2.6-10 mmol/l	100 (94,100)	84 (46, 98)
> 10.0 mmol/l	0 (0, 6)	16 (2, 54)
< 2.6 mmol/l	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Baseline sensor glucose	7.9 (6.9, 11.5)	8.2 (7.0, 12.4)
Mean sensor glucose (mmol/l)	6.2 (6.1, 7.1)	8.6 (7.4, 11.1)
SD of sensor glucose (mmol/l)	1.0 (0.8, 1.9)	1.3 (0.9, 2.5)
Episodes of blood glucose <2.6 mmol/l[b]	1	0
Insulin (U/kg/hour)	0.04 (0.03, 0.07)	0.02 (0.00, 0.11)
Nutritional intake		
Dextrose (mg/kg/min)	8.4 (7.2, 10.3)	8.5 (4.2, 10.6)
Protein (g/kg/day)	3.2 (2.5, 4.1)	3.5 (1.6, 4.1)
Lipid (g/kg/day)	1.8 (1.0, 1.8)	1.4 (0.9, 2.2)
Trophic feeds	4	4

What is 'Optimal'?

Hyperglycemia in Extremely Preterm Infants—Insulin Treatment, Mortality and Nutrient Intakes

Itay Zamir, MD[1], Andreas Tornevi, PhD[2], Thomas Abrahamsson, MD, PhD[3], Fredrik Ahlsson, MD, PhD[4], Eva Engström, MD, PhD[5], Boubou Hallberg, MD, PhD[6], Ingrid Hansen-Pupp, MD, PhD[7], Elisabeth Stoltz Sjöström, RD, PhD[8], and Magnus Domellöf, MD, PhD[1]

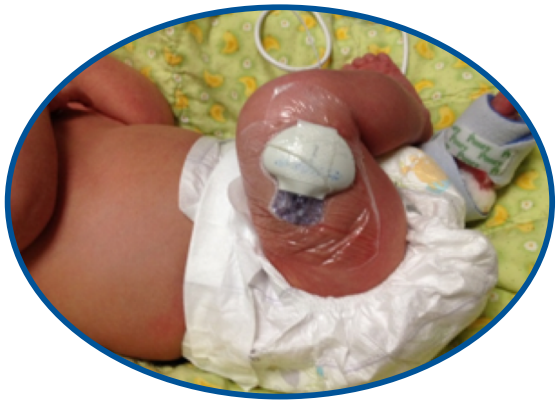
Table V. Logistic regression predicting the association between insulin treatment during the first 28 postnatal days and 28- and 70-day mortality in infants qualifying for different hyperglycemia definitions during the first 28 postnatal days (adjusted for gestational age and birth weight)

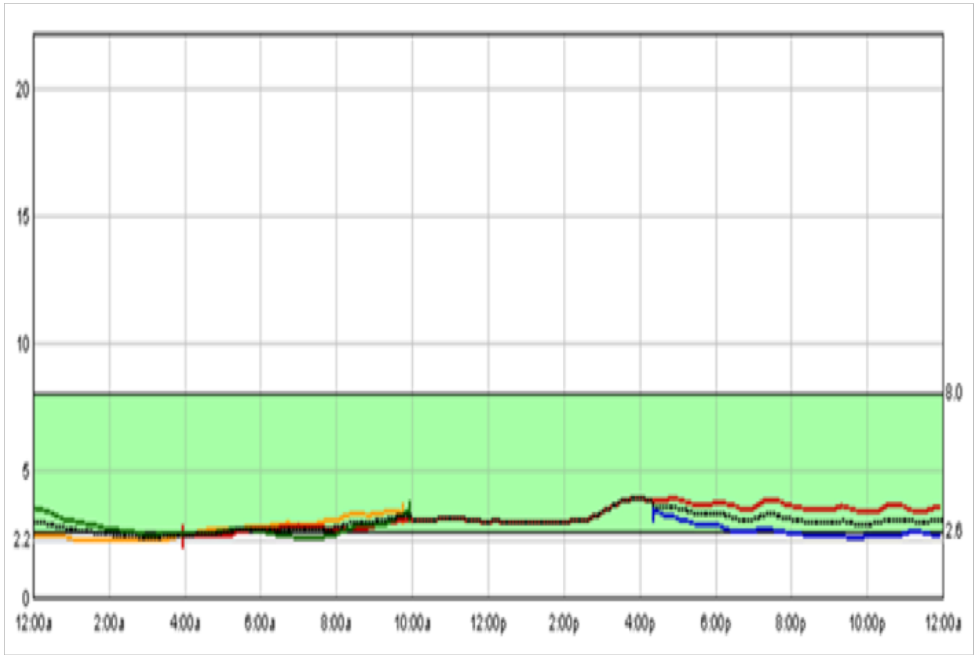
Hyperglycemia definition	Duration of hyperglycemia	Mortality among treated	Mortality among untreated	OR	95% CI	*P*
		28-d mortality				
>180 mg/dL (10 mmol/L)	1 d	3/80 (3.8%)	42/325 (12.9%)	0.180	.05-0.61	**.006**
	2 d	2/77 (2.6%)	22/175 (12.6%)	0.138	.03-0.61	**.009**
	3 d	2/65 (3.1%)	15/99 (15.2%)	0.139	.03-0.65	**.01**
>216 mg/dL (12 mmol/L)	1 d	2/78 (2.6%)	30/228 (13.2%)	0.122	.03-0.53	**.005**
	2 d	2/70 (2.9%)	14/98 (14.3%)	0.138	.03-0.65	**.01**
	3 d	2/50 (4.0%)	8/40 (20.0%)	0.160	.03-0.92	**.04**
		70-d mortality				
>180 mg/dL (10 mmol/L)	1 d	7/80 (8.8%)	50/325 (15.4%)	0.375	0.16-0.88	**.02**
	2 d	6/77 (7.8%)	28/175 (16%)	0.342	0.13-0.88	**.03**
	3 d	4/65 (6.2%)	19/99 (19.2%)	0.228	.07-0.72	**.01**
>216 mg/dL (12 mmol/L)	1 d	6/78 (7.7%)	37/228 (16.2%)	0.317	0.13-0.80	**.02**
	2 d	5/70 (7.1%)	19/98 (19.4%)	0.263	.09-0.76	**.01**
	3 d	3/50 (6.0%)	10/40 (25.0%)	0.182	.04-0.77	**.02**

The values marked in bold were statistically significant (<.05).

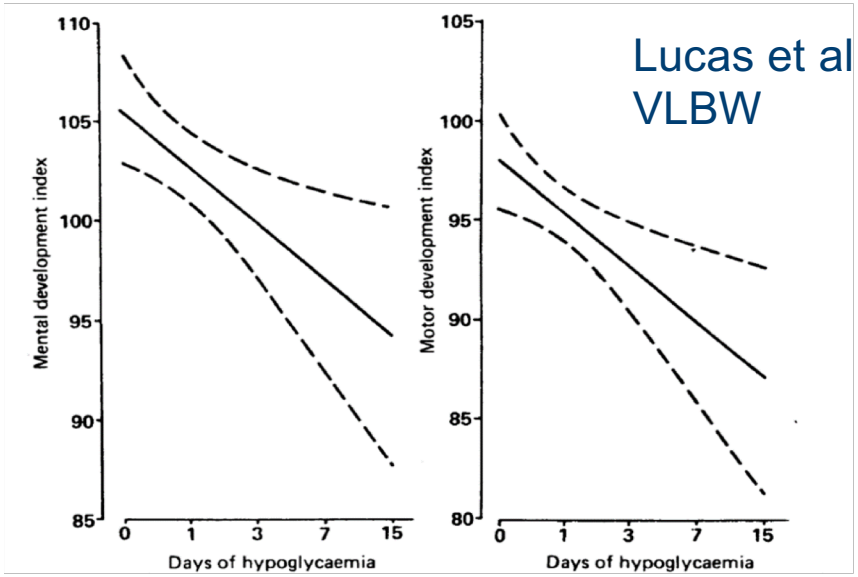
Metabolic Transition

'Hypoglycaemia'

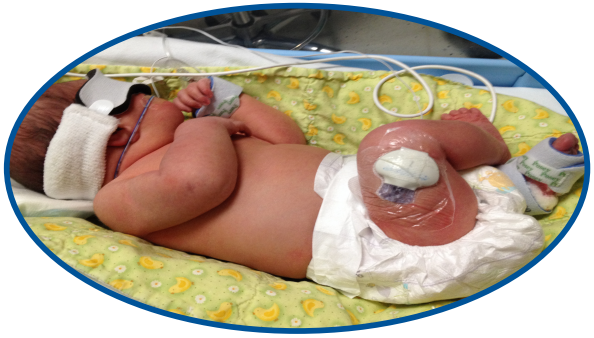




Hypoglycaemia



Lucas et al 1998 Preterm VLBW



Archives of Disease in Childhood, 1988, **63**, 1353–1358

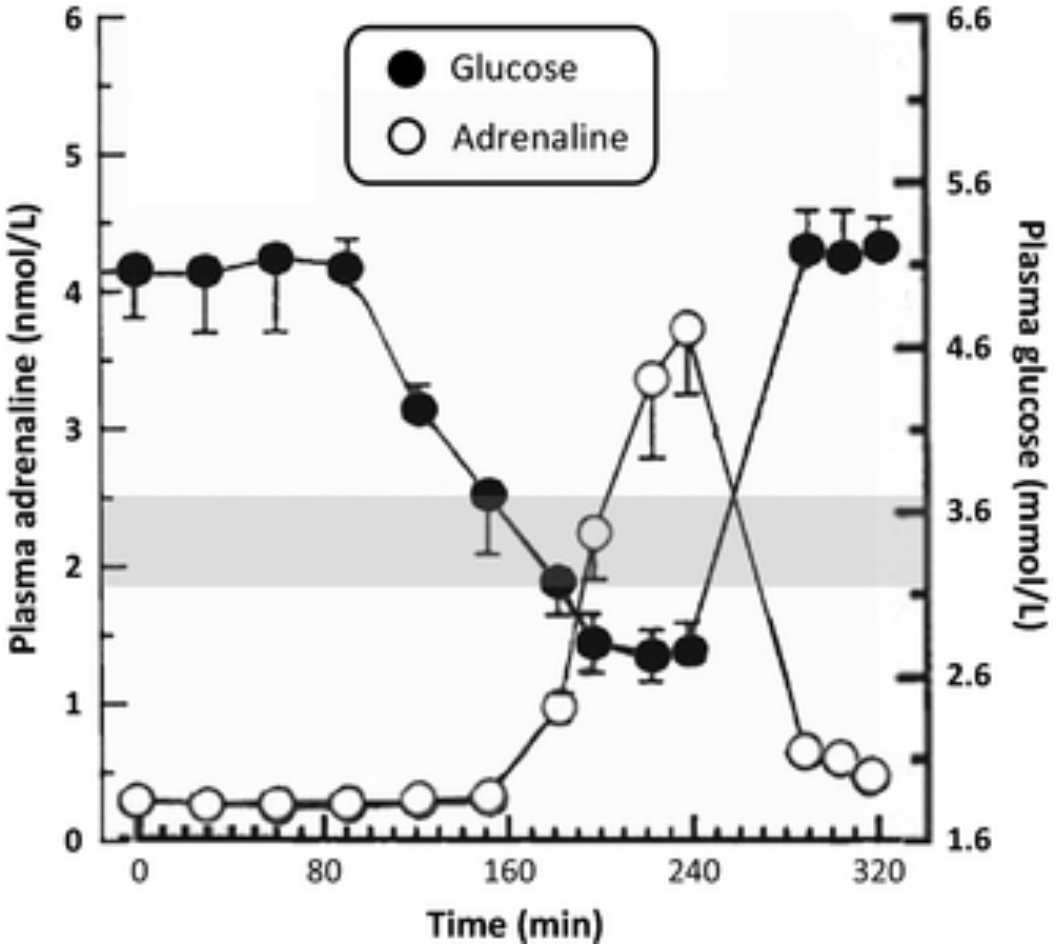
Neural dysfunction during hypoglycaemia

T H H G KOH, A AYNSLEY-GREEN, M TARBIT, AND J A EYRE

Department of Child Health, University of Newcastle upon Tyne

SUMMARY There is controversy over the definition of hypoglycaemia in neonates and children and over its significance when 'asymptomatic'. We measured sensory evoked potentials in relation to blood glucose concentration in 17 children: 13 were fasted or given insulin to investigate endocrine or metabolic abnormalities and four had spontaneous episodes of hypoglycaemia. Abnormal evoked potentials were recorded in 10 of the 11 children whose blood glucose concentration fell below 2·6 mmol/l; five of these 10 children were 'asymptomatic'. No change in evoked potentials was recorded in the six children whose blood glucose concentration remained above 2·6 mmol/l. Our findings suggest that the blood glucose concentration should be

Stress Response to hypoglycaemia



Adapted from Porcellati et al. Diabetes 2003

ARTICLE

15-Year Follow-Up of Recurrent "Hypoglycemia" in Preterm Infants

AUTHORS: Win Tin, FRCPCH,[a] Greta Brunskill, BSc,[b] Tom Kelly, PhD,[b] and Susan Fritz, SRN[c]

[a]*Department of Neonatal Medicine, James Cook University Hospital, Middlesbrough, United Kingdom;* [b]*Department of Neuropsychology, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom; and* [c]*The Northern Neonatal Nursing Initiative Trial Group, Regional Maternity Survey Office, Newcastle upon Tyne, United Kingdom*

KEY WORDS
hypoglycemia, preterm, developmental disabilities

www.pediatrics.org/cgi/doi/10.1542/peds.2012-0776

doi:10.1542/peds.2012-0776

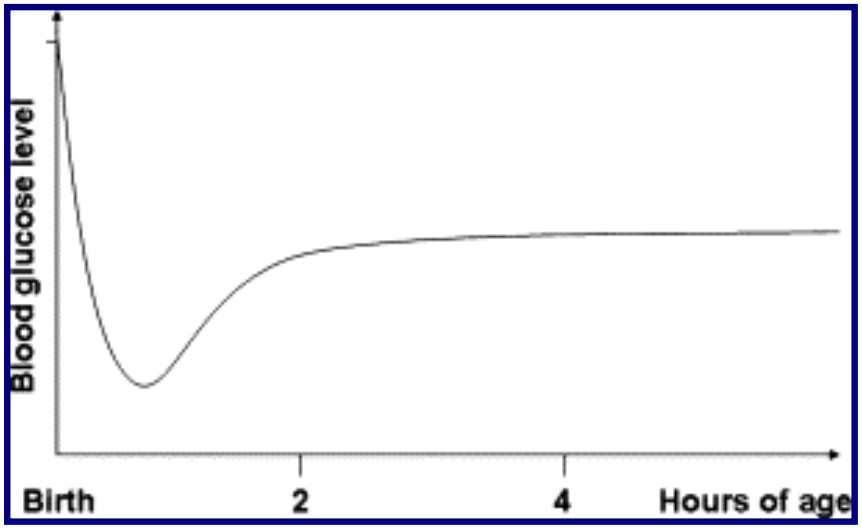
WHAT'S KNOWN ON THIS SUBJECT: It has been widely thought for the past 20 years that recurrent low blood glucose levels ≤2.5 mmol/L (45 mg/dL), even in the absence of any suggestive clinical signs, can harm a

WHAT THIS STUDY
outcome at 2 and
a blood glucose le
differ from that of

TABLE 2 Outcome at 2 y in All 47 Children Who Were Found to Have Had a Blood Glucose Level of ≤2.5 mmol/L at a Pre-Set Time on at Least 3 of the First 10 d of Life and in the 38 for Whom a Full Psychometric Assessment Was Possible 15 y Later and in Their Matched Controls (Who Never Had a Documented Low Level)

Measure	Index	Control[a]	Mean Paired Difference[b] (95% Confidence Interval)	No. of Pairs
Serious sensorimotor disability at age 2, *n* (%)	7 (14.9)	6 (12.8)	—	47
Cerebral palsy	6 (12.8)	4 (8.5)	—	47
Visually disabled	2 (4.2)	2 (4.2)	—	47
Uses hearing aids	1 (2.1)	1 (2.1)	—	47
Special educational provision at 10–15 y, *n* (%)				
Extra help in mainstream school	3 (6.5)	2 (4.3)	—	46
Attended a special school	4 (8.7)	4 (8.7)	—	46
Medication when 10–15 y old, *n* (%)				
On medication for asthma	5 (11.4)	5 (11.4)	—	45
On medication for epilepsy	2 (4.5)	2 (4.5)	—	45
Treated for severe behavior problems	2 (4.4)	4 (8.9)	—	45
Full psychometric assessment when ≥15 years old, mean ± SD				
Full-scale IQ (short Wechsler-III)	80.7 ± 19.8	81.2 ± 15.2	−0.6 (−8.3 to 7.2)	38
Reading (Wechsler WORD score)	91.1 ± 18.3	90.2 ± 15.9	+0.9 (−7.5 to 9.2)	36
Numeracy (Wechsler WOND score)	84.8 ± 21.4	83.9 ± 17.4	+0.9 (−7.5 to 9.4)	35
Behavior (total Achenbach score)	51.0 ± 10.2	54.4 ± 13.8	−3.2 (−9.3 to 2.9)	37
Adaptation to Daily Living (Vineland)	74.4 ± 19.1	68.5 ± 16.7	+5.9 (−2.8 to 14.7)	37

Metabolic Adaptation



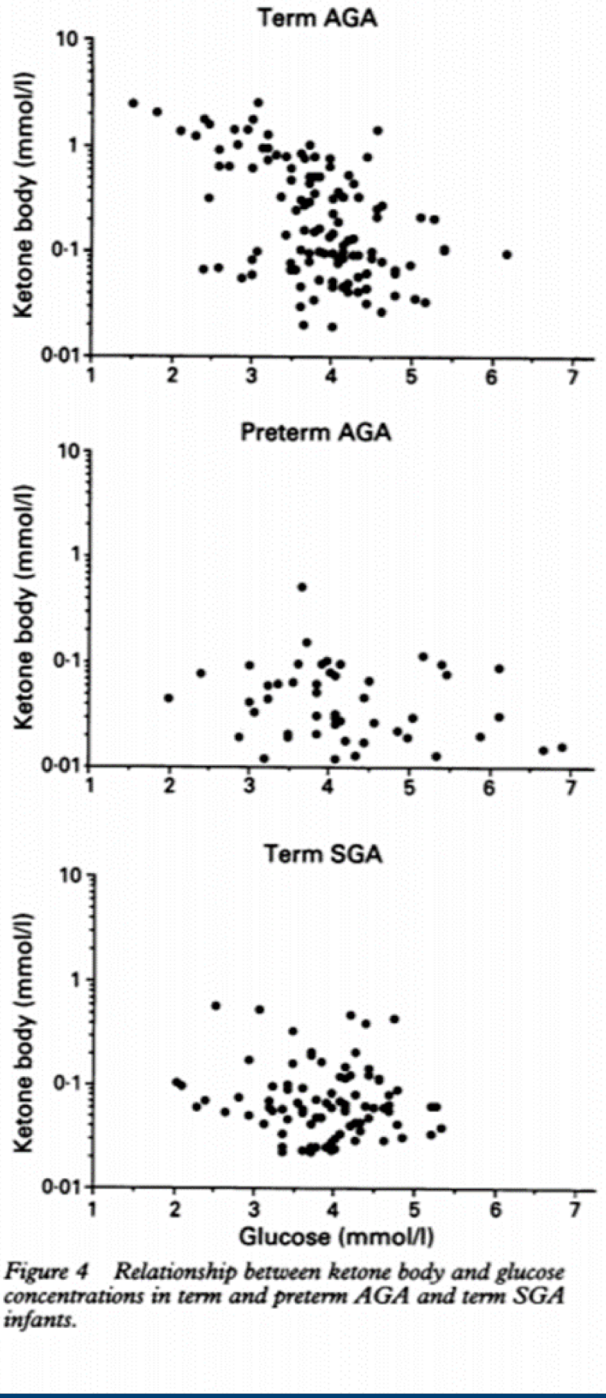
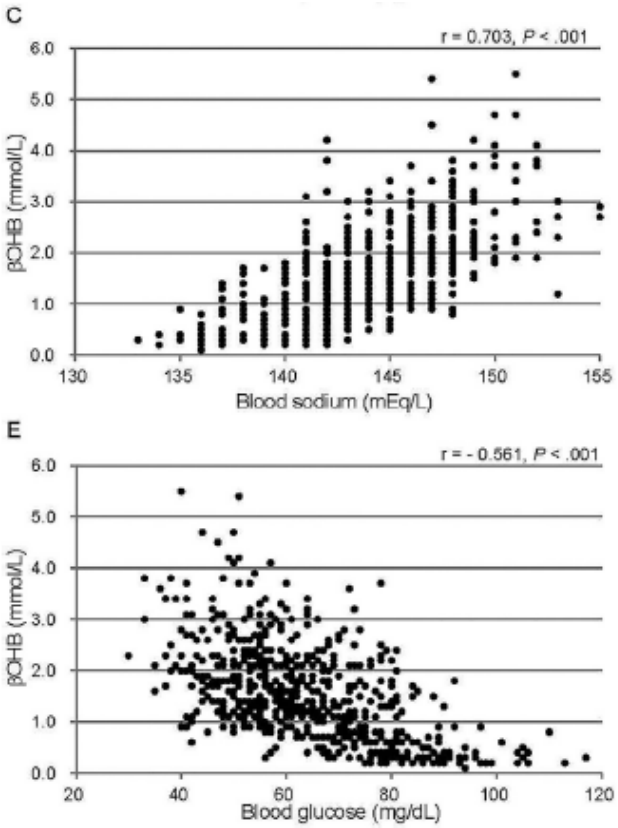


Figure 4 Relationship between ketone body and glucose concentrations in term and preterm AGA and term SGA infants.

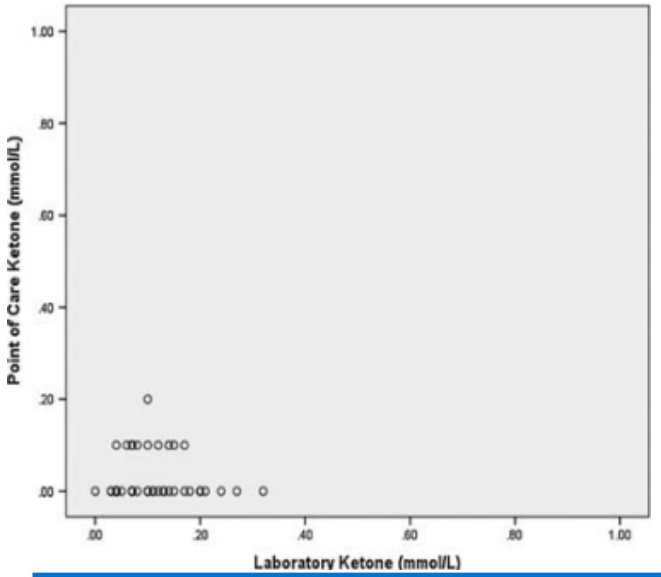
Hawdon et al ADC 1993

Whose at risk? Measuring Alternative Fuels

Term AGA vs Infants at risk infants



Futatani J Peds 2017



K Crawford et al 2016

POCKET: Feasibility of Point of Care measurement of Ketones

Point of Care

•Cornblath Operational Thresholds (2000)
>2 BG level <2 mmol/L (36 mg/dL)
≥1 BG <2.5 mmol/L (45 mg/dL) with abnormal clinical signs
≥1 BG <1.0 mmol/L (<18 mg/dL) needs iv to increase to plasma glucose > 2.5 mmol/L (45 mg/dL)
Documented hyperinsulinic hypoglycaemia > 3.5 mmol/L (60 mg/dL)

•The American Academy of Pediatrics (AAP) (2011)
1.4-2.2 mmol/L (25-40 mg/dL) in the first 4 hours,
1.9-2.5 mmol/L (35-45mg/dL) from 4-24 hours
2.5 mmol/L (45 mg/dL) after 24 hours.[11]

•The Paediatric Endocrine Society (2015)
>2.8 mmol/L (50 mg/dL) during the first 48 hours
>3.3 mmol/L (60 mg/dL) for infants older than 48 hours.[8]

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Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds

Marvin Cornblath, Jane M. Hawdon, Anthony F. Williams, Albert Aynsley-Green, Martin P. Ward-Platt, Robert Schwartz and Satish C. Kalhan

Pediatrics 2000;105;1141-1145
DOI: 10.1542/peds.105.5.1141

'*It should be underscored that the* ***therapeutic objective*** ***(plasma glucose >45 mg/dL, 2.5 mmol/L)*** *is quite different from the operational threshold for intervention (36 mg/ dL, 2.0 mmol/L).*

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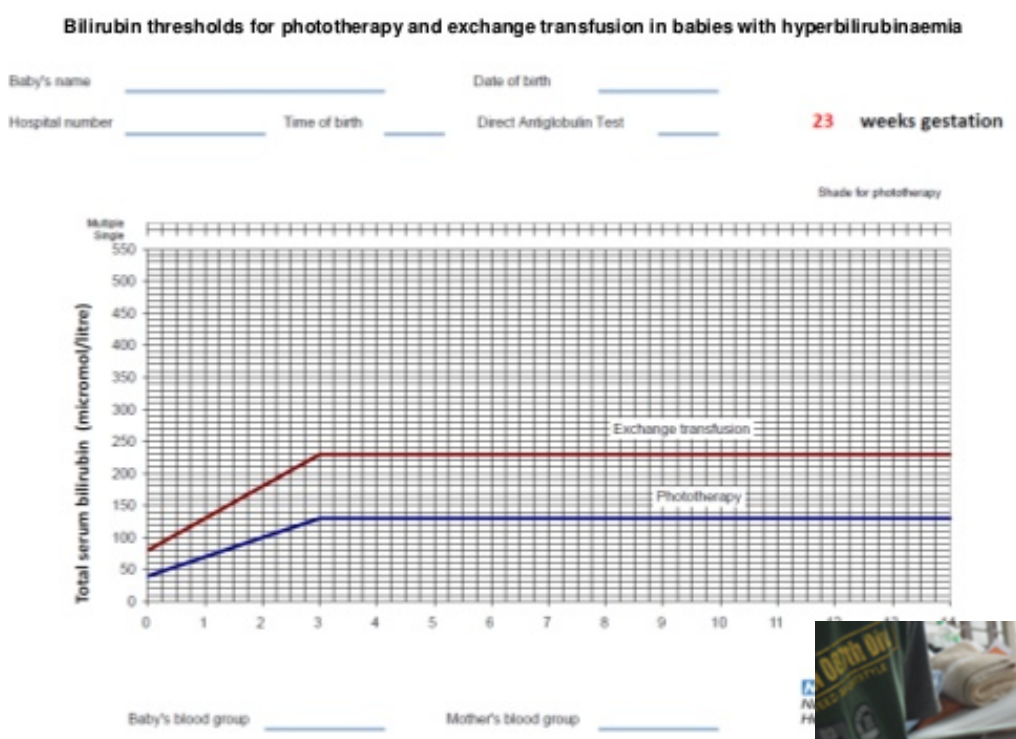

Definitions
Interventions
Pathology

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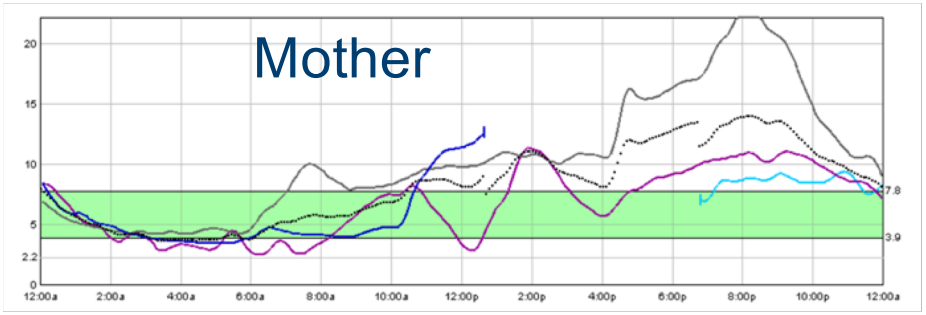
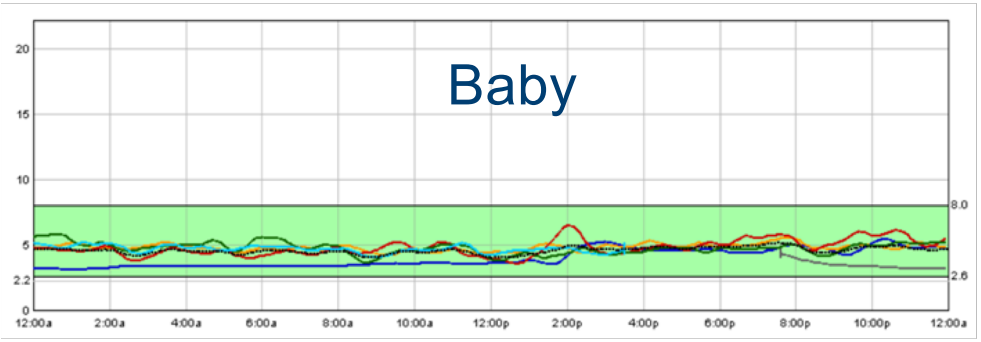
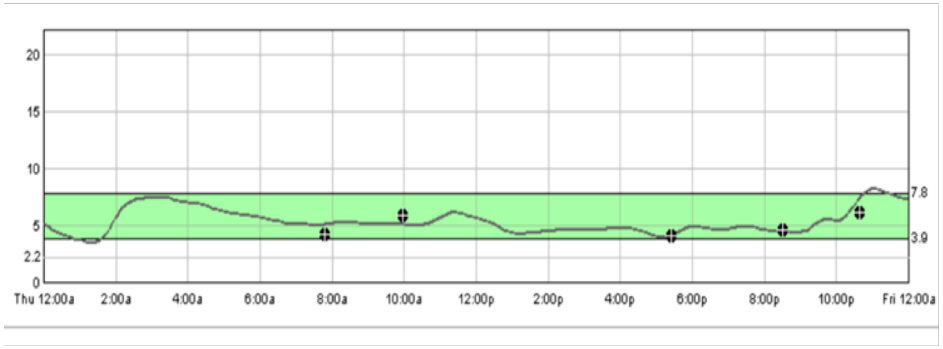
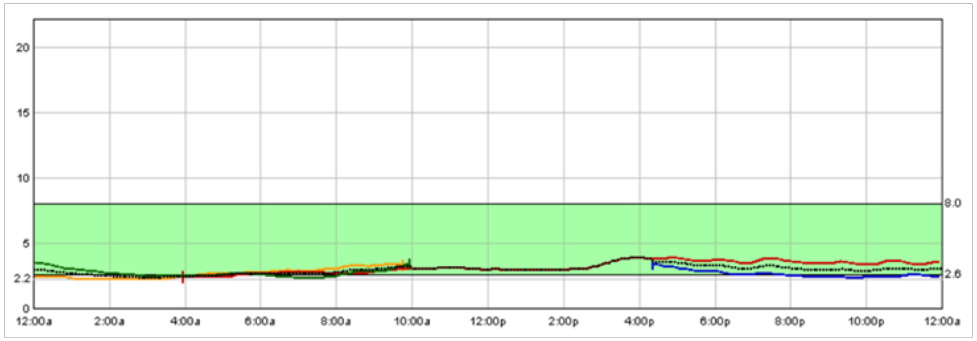
CONCEPTT

Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT)









SG <2.6mmol/l - 25% of babies spent >50% of first 24 hours
Day 3 up to 21% of time

Babies with higher % time <2.6mmol/L were those <u>not</u> treated with IV dextrose

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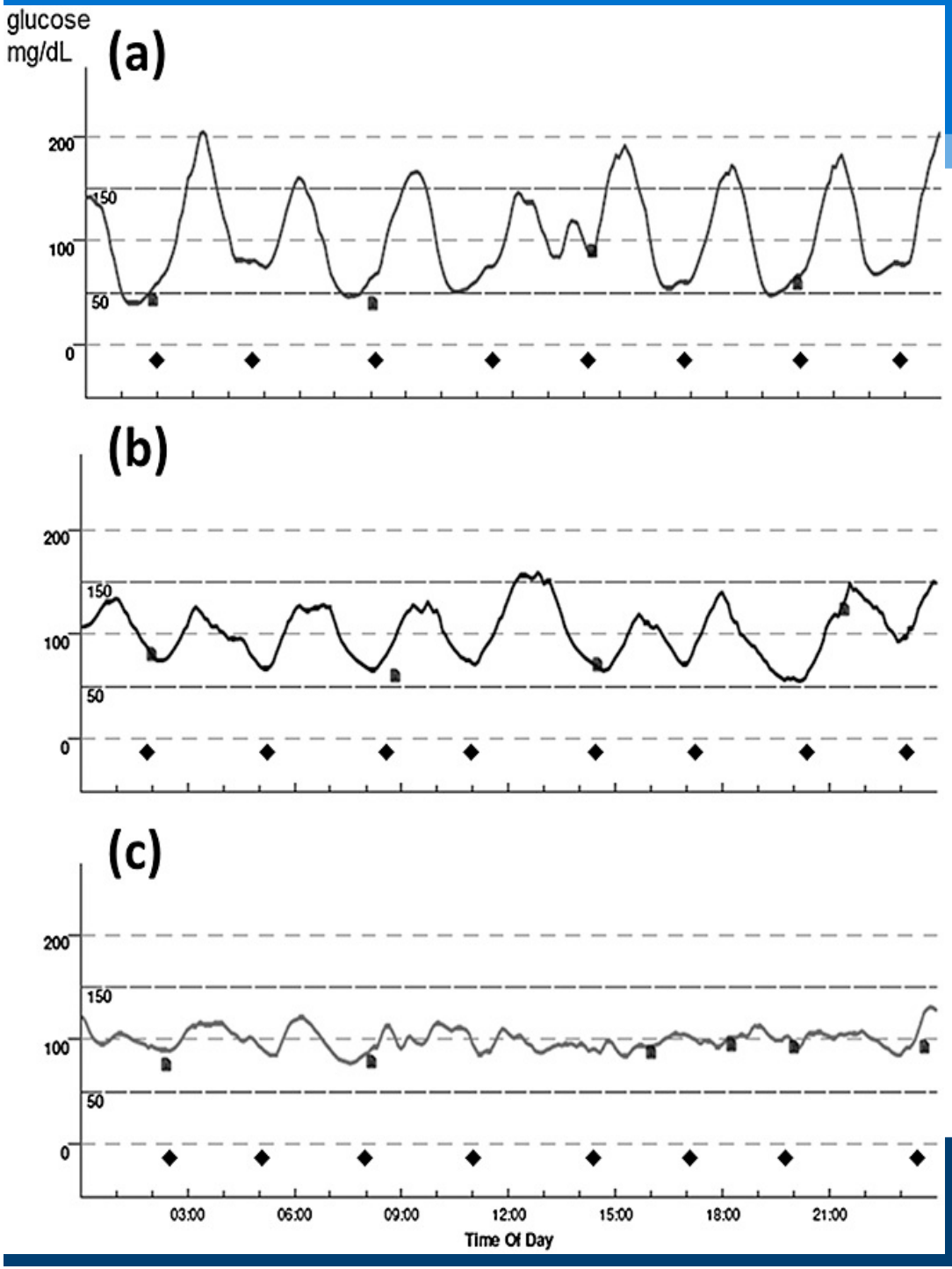


CGM
Corrected GA 33 weeks
On 3 hourly feeds

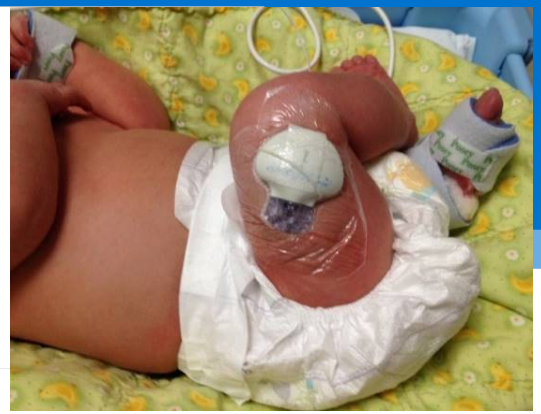
8 infants (62%)
repeated hyperglycemic (>150 mg/dL)
and hypoglycemic (<50 mg/dL) events.

Mizumoto 2015
Pediatrics International

JAMA Pediatrics | Original Investigation

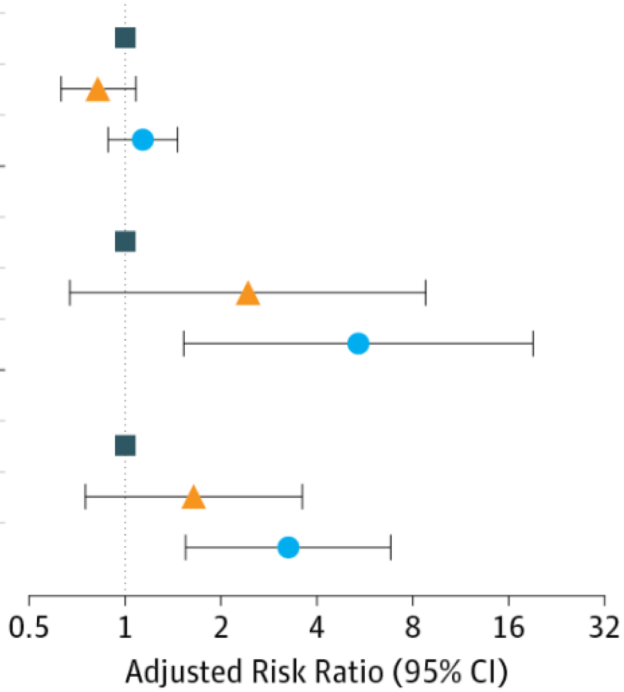
Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years

Christopher J. D. McKinlay, PhD; Jane M. Alsweiler, PhD; Nicola S. Anstice, PhD; Nataliia Burakevych, PhD; Arijit Chakraborty, PhD; J. Geoffrey Chase, PhD; Gregory D. Gamble, MSc; Deborah L. Harris, PhD; Robert J. Jacobs, PhD; Yannan Jiang, PhD; Nabin Paudel, PhD; Ryan J. San Diego, MSc; Benjamin Thompson, DPhil; Trecia A. Wouldes, PhD; Jane E. Harding, DPhil; for the Children With Hypoglycemia and Their Later Development (CHYLD) Study Team



A Severity

Hypoglycemia category	No./Total No. (%)	*P* Value
Neurosensory impairment		
Normoglycemia	75/195 (38.5)	
Mild hypoglycemia	53/167 (31.7)	.07
Severe hypoglycemia	51/111 (46.0)	
Visual-motor difficulty		
Normoglycemia	3/194 (1.6)	
Mild hypoglycemia	5/167 (3.0)	.04
Severe hypoglycemia	8/110 (7.3)	
Executive dysfunction		
Normoglycemia	9/190 (4.7)	
Mild hypoglycemia	12/165 (7.3)	.02
Severe hypoglycemia	17/108 (15.7)	



JAMA Pediatr. 2017;171(10):972-983. doi:10.1001/jamapediatrics.2017.1579

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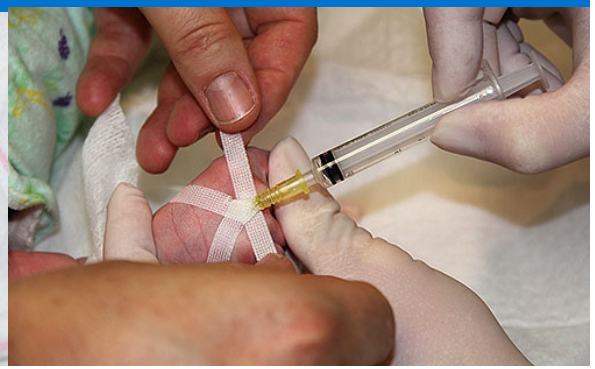
Interventions

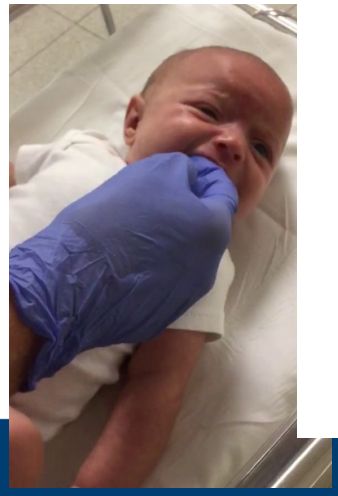


Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial

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

Summary



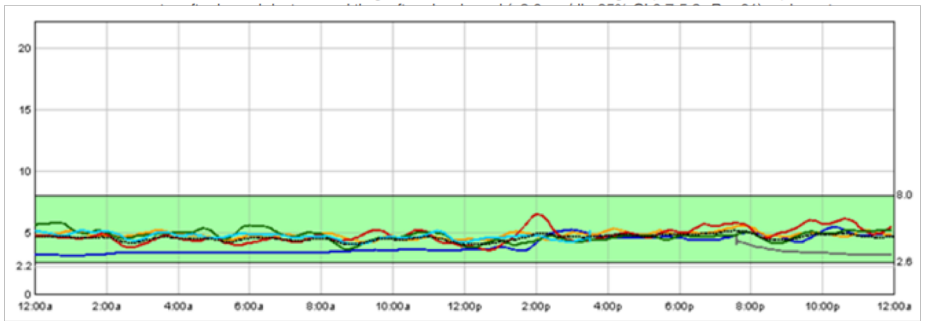
Glucose Variability?

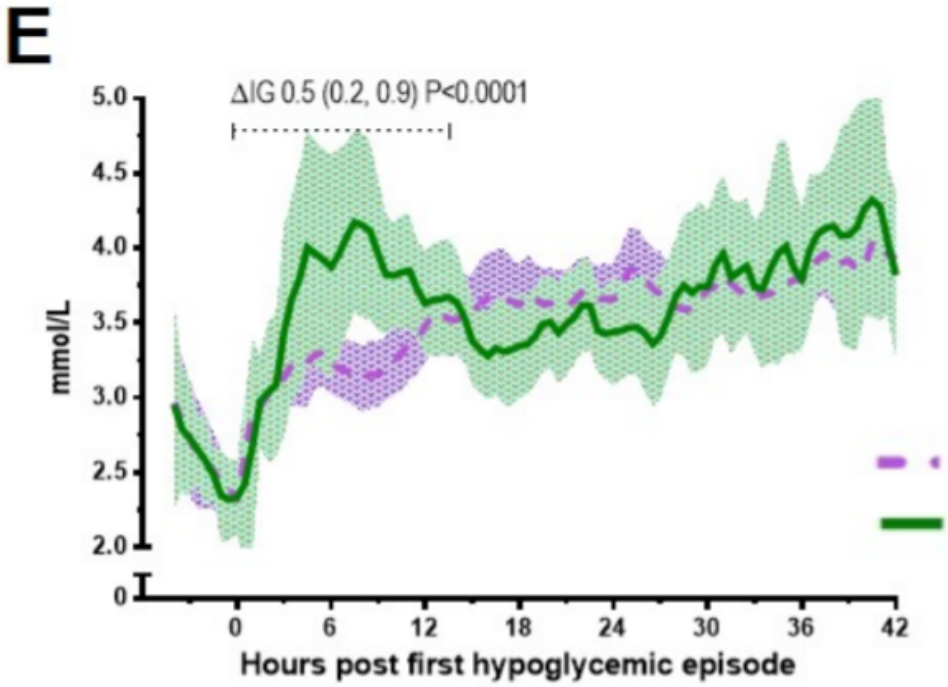
ORIGINAL ARTICLES
www.jpeds.com • THE JOURNAL OF PEDIATRICS

What Happens to Blood Glucose Concentrations After Oral Treatment for Neonatal Hypoglycemia?

Deborah L. Harris, PhD[1,2], Greg D. Gamble, MSc[2], Philip J. Weston, MBChB[1], and Jane E. Harding, DPhil[2]

Objective To determine the change in blood glucose concentration after oral treatment of infants with hypoglycemia in the first 48 hours after birth.
Study design We analyzed data from 227 infants with hypoglycemia (blood glucose <46.8 mg/dL, 2.6 mmol/L) born at a tertiary hospital who experienced 295 episodes of hypoglycemia. 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.
Results The overall mean increase in blood glucose concentration was 11.7 mg/dL (95% CI 10.4-12.8). The in-





Normal 2 y and 4.5 y

Normal 2y, Neurosensory Impairment 4.5 y

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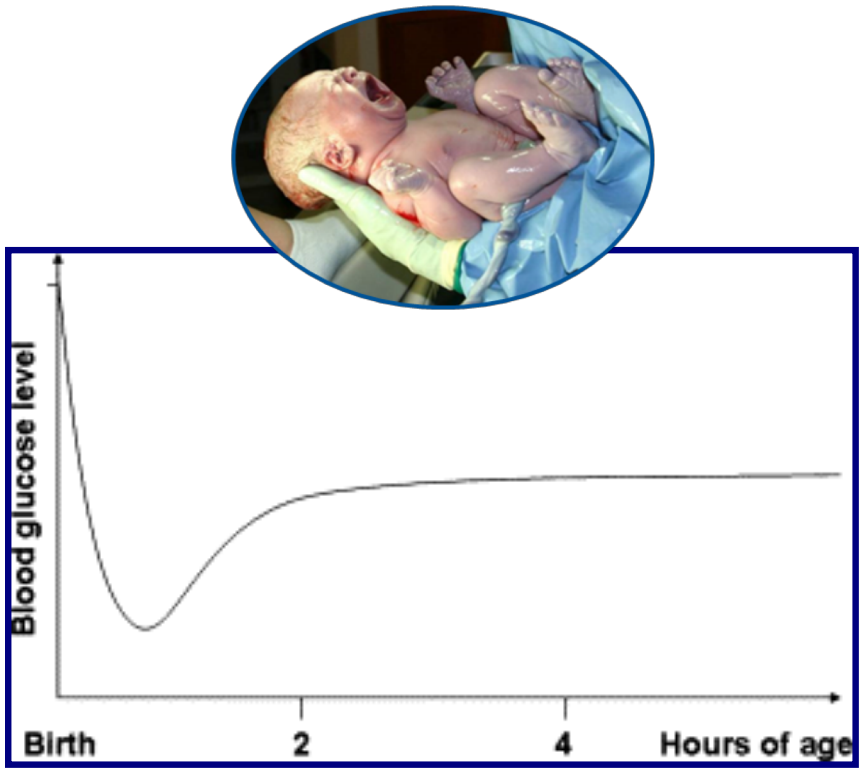
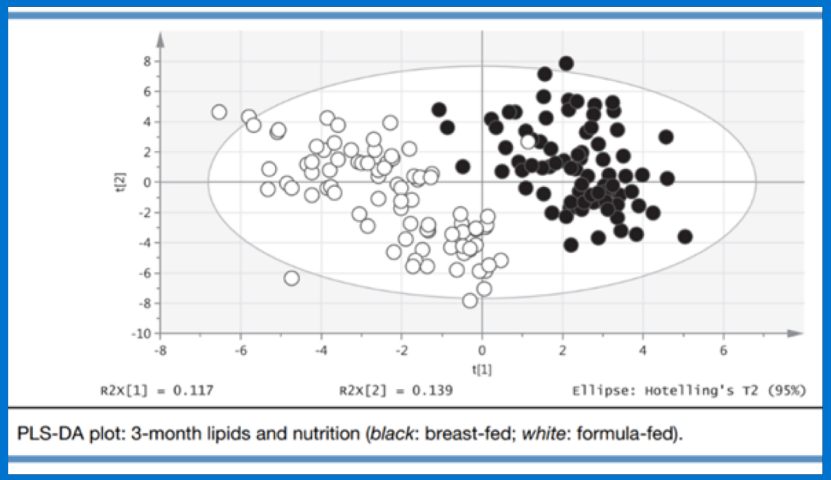
Long Term Consequences

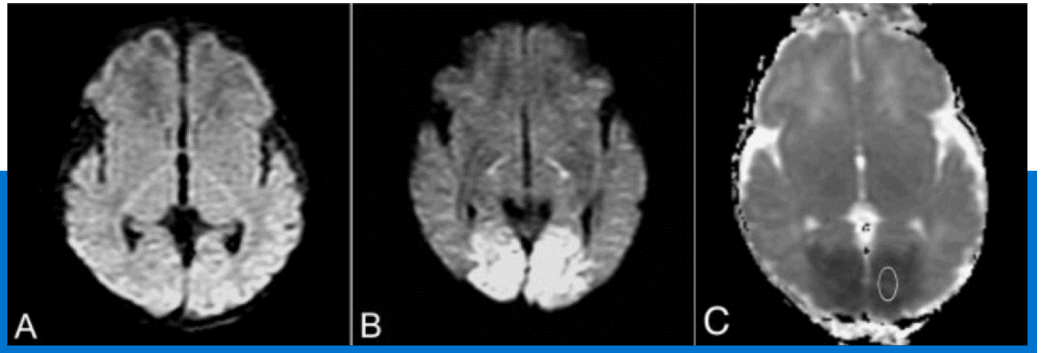
Physiology allows adaptive adjustments to new challenges

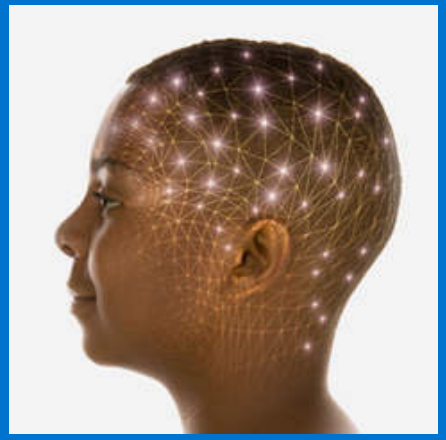


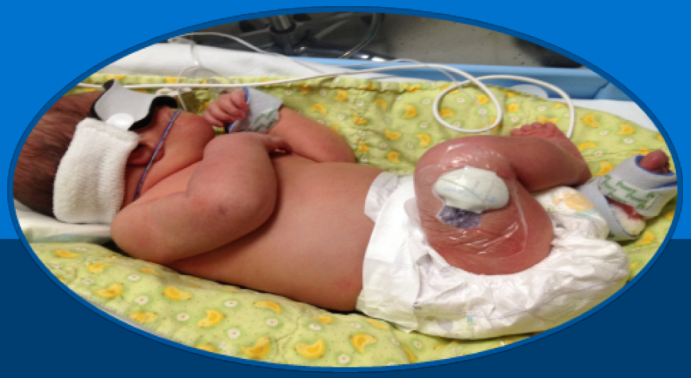
Clinical Significance?



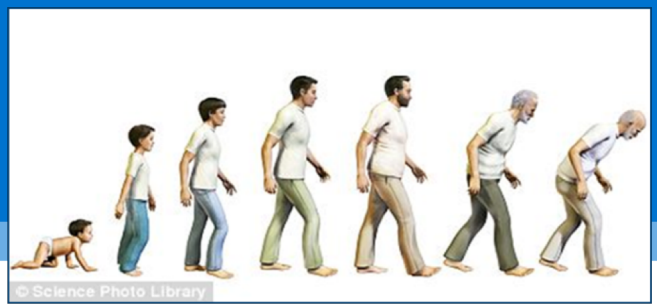
PLS-DA plot: 3-month lipids and nutrition (*black*: breast-fed; *white*: formula-fed).







Metabolic Adaptation



Developmental challenges - long term impact

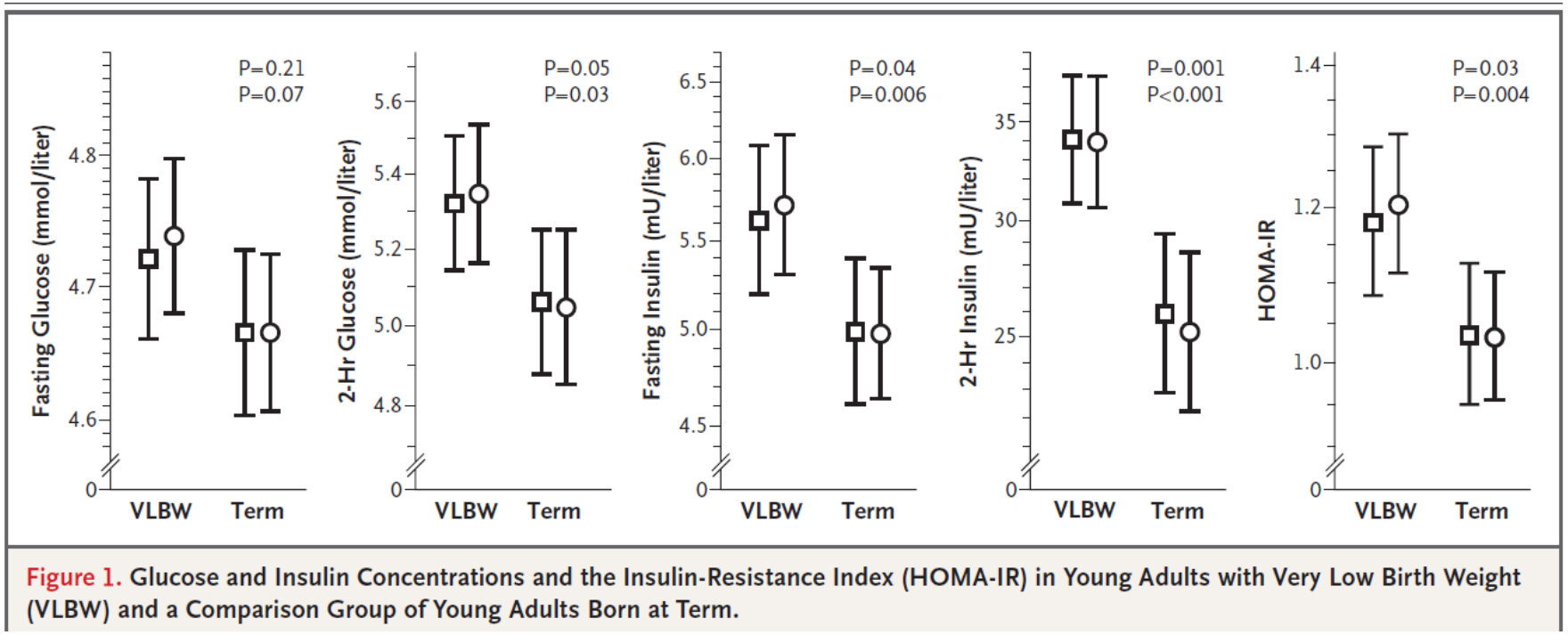


Figure 1. Glucose and Insulin Concentrations and the Insulin-Resistance Index (HOMA-IR) in Young Adults with Very Low Birth Weight (VLBW) and a Comparison Group of Young Adults Born at Term.

Glucose Regulation in Young Adults with Very Low Birth Weight

Petteri Hovi, M.D., Sture Andersson, M.D., Ph.D.,

Components of the Metabolic Syndrome in Early Childhood in Very-Low-Birth-Weight Infants

Miranda de Jong[a] Harrie N. Lafeber[b] Anneke Cranendonk[b]
Mirjam M. van Weissenbruch[b]

Table 2. Presence of the metabolic syndrome components at the corrected age of 2 years

	Girls (n = 19)	Boys (n = 19)	Standard care (n = 21)	Early insulin (n = 17)
BMI SDS >2	0/19	0/19	0/21	0/17
Systolic BP ≥90th percentile	3/15, 20.0%	4/17, 23.5%	2/18, 11.1%	5/14, 35.7%
Diastolic BP ≥90th percentile	5/15, 33.3%*	15/17, 88.2%*	9/18, 50.0%	11/14, 78.6%
Systolic and/or diastolic BP ≥90th percentile	5/15, 33.3%**	15/17, 88.2%**	9/18, 50.0%	11/14, 78.6%
Glucose ≥5.6 mmol/l	0/19	0/19	0/21	0/17
HDL cholesterol ≤1.03 mmol/l	5/18, 27.8%	7/19, 36.8%	7/21, 33.3%	5/16, 31.3%
Triglycerides ≥0.98 mmol/l	6/18, 33.3%	5/19, 26.3%	10/21, 47.6%***	1/16, 6.3%***
One metabolic syndrome component present	6/19, 31.6%	5/19, 26.3%	6/21, 28.6%	5/17, 29.4%
Two metabolic syndrome components present	5/19, 26.3%	8/19, 42.1%	7/21, 33.3%	6/17, 35.3%
Three metabolic syndrome components present	0/19	2/19, 10.5%	2/21, 9.5%	0/17

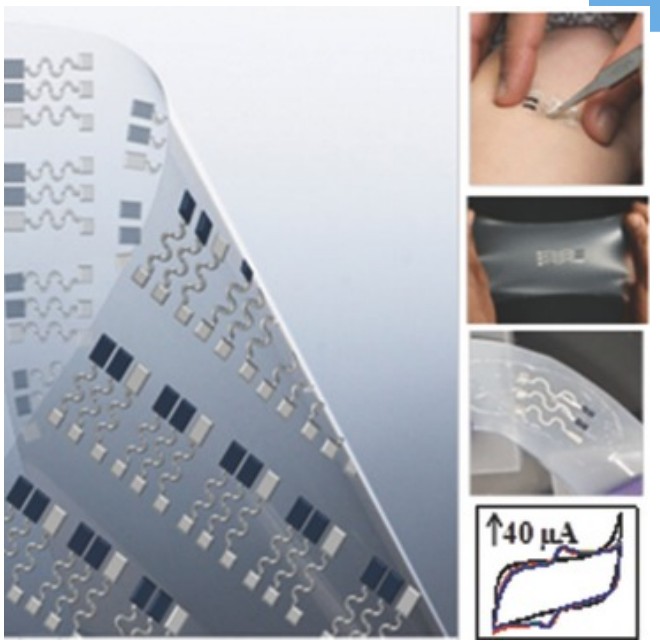
Horm Res Paediatr 2014;81:43–49

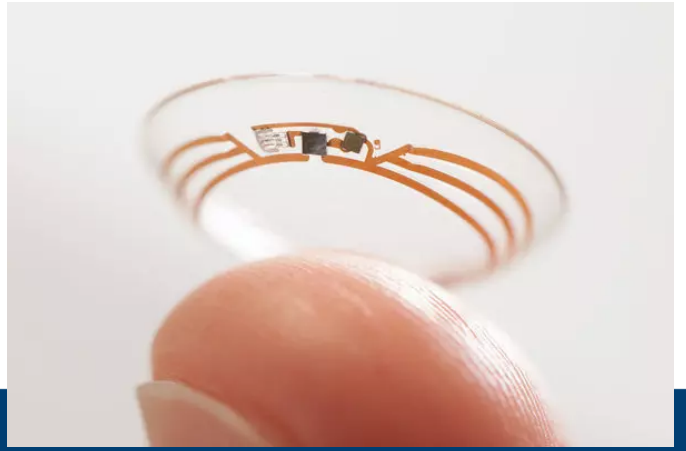
Continuous glucose monitoring in the neonatal intensive care unit: not quite ready for 'plug and play'

Teri L Hernandez,[1,2] William W Hay Jr,[3] Paul Joseph Rozance[3]

In the very low birthweight (VLBW) infant population, high glucose concentrations have been associated with increased mortality, brain injury, retinopathy of prematurity and worse neurodevelopmental outcomes. However, trials to

clinical guideline dictating care decisions based on the CGM values versus standard neonatal care. In the standard care arm, infant interstitial glucose concentrations were measured with a blinded retrospective recording CGM (iPro2, Medtronic

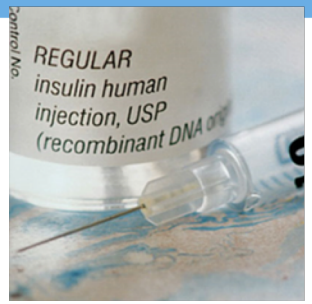




Glucose is an Acute Biomarker

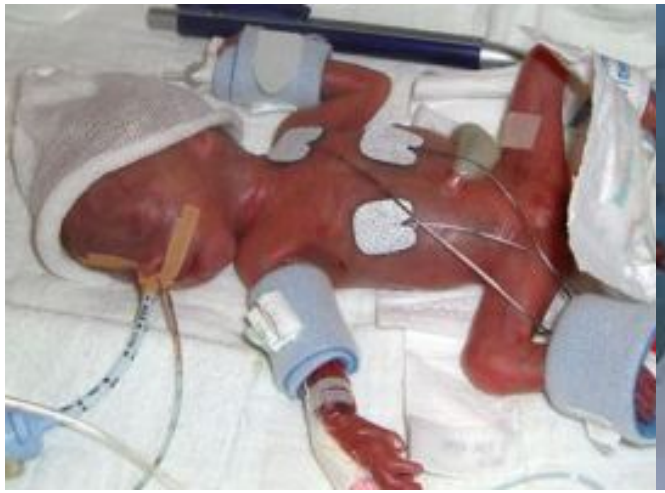
Hypoglycaemia

Line dislodged
Nutrition
Sepsis
Drugs
Endocrine



Hyperglycaemia

Sepsis
Nutrition
Catabolism
Drugs
Inflammation
Endocrine

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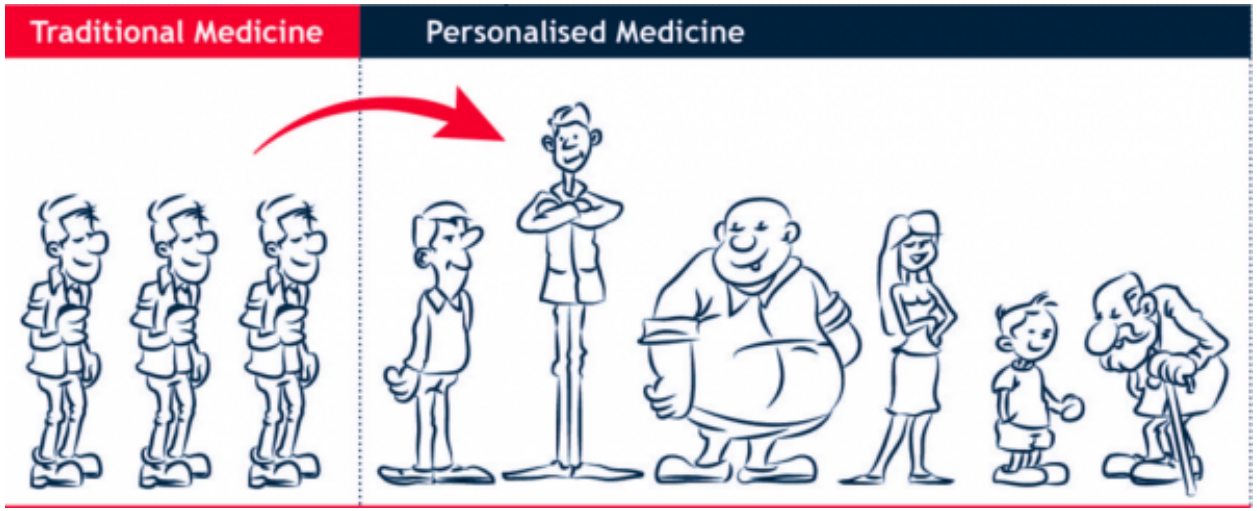
Traditional Medicine
Personalised Medicine

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NIRTURE FU
Ruben Willemsen

What is 'Optimal'?

Clinical Observations

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Increasing Early Protein Intake Is Associated With a Reduction in Insulin-Treated Hyperglycemia in Very Preterm Infants

Ajit Mahaveer, MRCPCH; Christopher
Colin Morgan, MD, FRCPCH, MRCP

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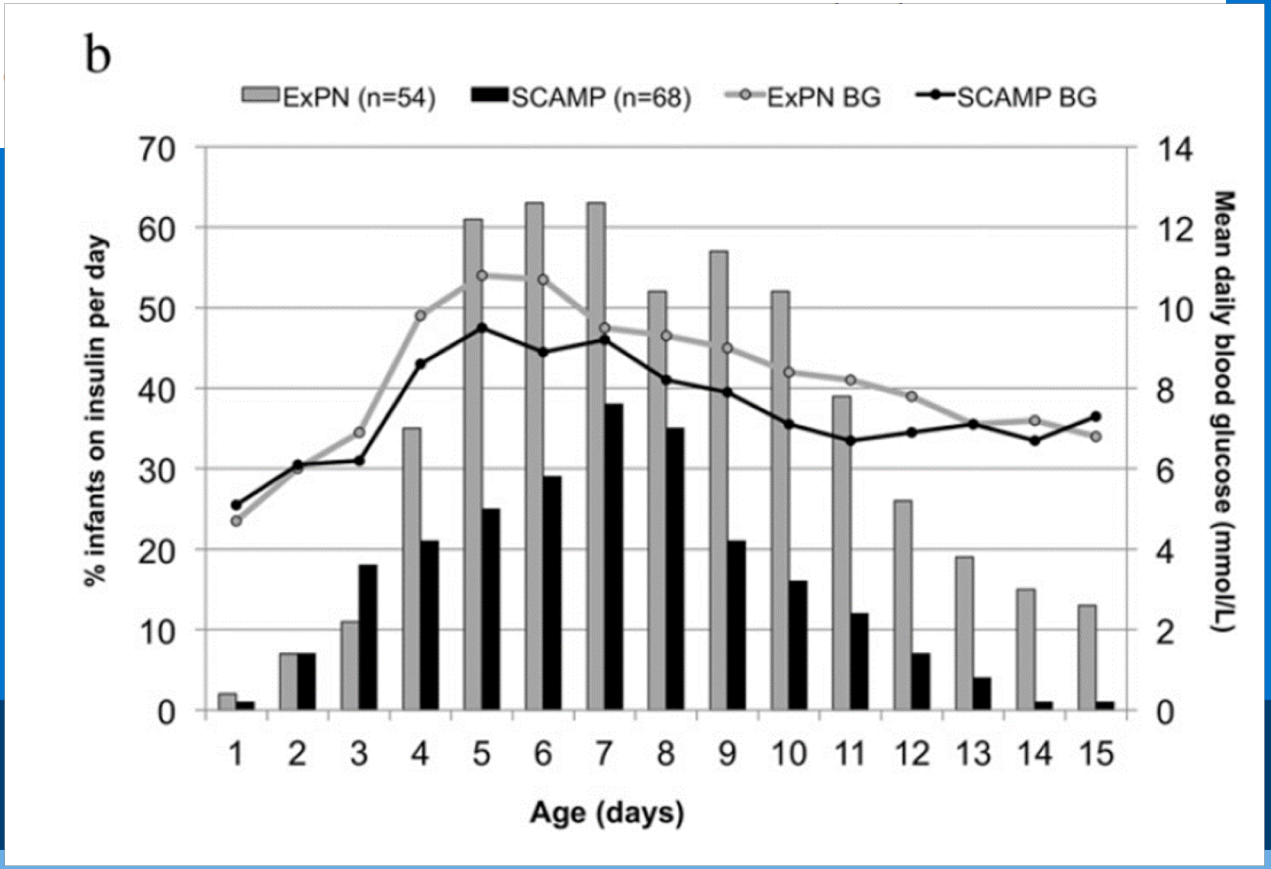

Neonatal Morbidities and Developmental Delay in Moderately Preterm-Born Children

Variable	Univariate Analyses		Multivariate Analyses[a]	
	OR (CI)	*P*	OR (CI)	*P*
Birth-related				
Low Apgar score	1.11 (0.33–3.75)	.87	—	—
Asphyxia	3.18 (1.01–10.0)	.05	2.67 (0.74–9.60)	.13
Admission-related				
Not admitted to a pediatric ward	0.81 (0.10–6.59)	.85	—	—
Tertiary NICU	1.74 (0.96–3.15)	.07	1.22 (0.61–2.42)	.57
Transportation	1.26 (0.43–3.15)	.67	—	—
Other neonatal				
Circulatory insufficiency	0.47 (0.05–3.05)	.38	—	—
Respiratory insufficiency				
CPAP	0.85 (0.44–1.67)	.65	—	—
Ventilation	1.04 (0.45–2.64)	.84	—	—
CPAP and/or ventilation	0.76 (0.39–1.48)	.65	—	—
Apnea	0.85 (0.44–1.67)	.65	—	—
Caffeine	0.76 (0.39–1.48)	.41	—	—
Septicemia	1.56 (0.53–4.60)	.42	—	—
Hypoglycemia[b]	2.42 (1.23–4.77)	.01	2.19 (1.08–4.46)	.03
Hyperbilirubinemia[c]	1.52 (0.94–2.46)	.09	1.48 (0.89–2.46)	.13
Biological and environmental factors				
SGA (<10th percentile)	3.30 (1.78–6.12)	<.001	2.62 (1.36–5.05)	<.001
Male gender	3.54 (1.94–6.46)	<.001	3.12 (1.70–5.75)	<.001
Low gestational age[d]	0.95 (0.57–1.60)	.85	—	—
Low maternal education	1.31 (0.79–2.18)	.30	—	—

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Original Investigation

Association Between Transient Newborn Hypoglycemia and Fourth-Grade Achievement Test Proficiency
A Population-Based Study

Jeffrey R. Kaiser, MD, MA; Shasha Bai, PhD; Neal Gibson, PhD; Greg Holland, PhD; Tsai Mei Lin, MS; Christopher J. Swearingen, PhD; Jennifer K. Mehl, MD; Nahed O. ElHassan, MD

Editorial page 892
Supplemental conten

IMPORTANCE Prolonged neonatal hypoglycemia is associated with poor long-term

n= 1395 newborns data linked to school tests

Transient hypoglycemia -only 1 measure
BG <35 mg/dL(6%) BG <45 mg/dL(19%))

After adjusting for cofounders a ***single measurement***

Associated with 50% decreased proficiency on 4th grade assessments
Literacy OR 0.49 (0.28-0.83) and 0.62 (0.45-0.85),
Mathematics OR 0.49 (0.29-0.82) and 0.78 (0.57-1.08)

Kaiser JAMA Peds 2015

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Hyperglycaemia as a marker of Catabolism