“Sweet As”
Neonatal Hypoglycaemia

Dr Gillian Opie
Neonatal Paediatrician, IBCLC
Mercy Hospital for Women
Heidelberg, Victoria.
Learning Objectives

• Understand glucose physiology and biochemistry
• Know symptoms of hypoglycaemia
• Definition and evidence
• Measurement and screening
• Infant of the diabetic mother (IDM)
• ABM protocol
BRAIN food

Image: northernrockiesneurosurgeons
Glucose and Brain

- Brain cells in normal state only use glucose for energy.
- In fasted state can use fats with difficulty.
- Brain cells absorb glucose directly from blood and do not require assistance of insulin. :: exquisitely sensitive to circulating glucose level.
Glucose: Regulatory Hormones

Pancreas: Islets of Langerhans

- Insulin – β cells
- Glucagon – α cells
- Somatostatin - δ cells
- Cortisol
- Growth hormone
- Adrenaline
Glucose regulation

- Eat ⇒ ↑glucose ⇒ ↑insulin
- Insulin promotes glucose storage in liver and muscle as glycogen and liver fat.

- ↓glucose ⇒ ↓insulin ⇒ ↑glucagon
- Glucagon promotes glycogen conversion to glucose and release from liver
- If insufficient glycogen or glucose insulin promotes fat utilisation
Hypothalamus: glucose regulation

Severe hypoglycaemia
• stimulates adrenaline release

Prolonged hypoglycaemia
• Growth hormone
• Cortisol
• Facilitate fat utilisation for energy
Blood glucose

Glucose  UDP

Glycogen

Gluc-1-Phosphate

Gluc-6-Phosphate

Pyruvate

Acetyl Coenzyme A

Citric Acid / Krebs Cycle

Oxaloacetic acid

ATP = ENERGY

Cell Membrane
Ketone Bodies

- arise from fatty acid metabolism
- 3 compounds
  - Acetoacetic acid
  - $\beta$ hydroxybutyric acid
  - Acetone

- In starvation no carbohydrates are available and energy must come from fats.
Fetal Glucose Metabolism:

- All fetal glucose needs met by placenta
- Pancreas present from early gestation: 4W
- Insulin not active in glucose regulation
- Insulin acts as anabolic hormone

- Fetal pancreas responds to high maternal glucose levels with hypertrophy of pancreatic islet cells and increased fetal insulin content
Birth

Umbilical cord cutting

↑ glucagon ↑ adrenaline

Circulating insulin levels fall and remain low for several days

Sensitivity of hormonal receptors change

Neonatal enzyme activity matures

Favours glycogenolysis, lipolysis, and gluconeogenesis
Neonatal Hypoglycaemia

not in itself a medical condition but can be an indication of underlying illness or a failure to adapt physiologically to the outside world at birth

Hypoglycaemia - symptoms

- Jitteriness
- Lethargy
- Feeding intolerance
- Apnoea
- Cyanosis
- Seizures
Srinivasan (1986) 344 term infants

- cord glucose 3.3 mmol/l
- 1 hour 1.4 mmol/l
- 2 hours 2.3 mmol/l

Cornblath 1975

- < 1.66 mmol/l based on studies of fasted infants
- incidence term 4.4 per 1000
- LBW 15.5 per 1000

Lucas 1988

- preterm infants BG < 2.6 mmol/l
- reduced mental & motor development 18 M
Symptomatic Hypoglycaemia

MRI depicted taken on day 6 of life.

Loss grey white matter differentiation,
Low signal in basal ganglia (long arrow)

Increased signal intensity (arrowhead)
R frontal region
L posterior region

Neurodevelopmental outcome poor
L hemiplegia
Microcephaly
Epilepsy

Symptomatic Hypoglycaemia

- Patterns of cerebral white matter injury seen after symptomatic hypoglycaemia associated with neurologic dysfunction are varied.

Early MRI findings are more instructive than severity or duration of hypoglycaemia for predicting neurodevelopmental outcomes.

Operational thresholds

• Level at which intervention should be considered

• Significant hypoglycaemia cannot be defined by a single number RATHER it is a value unique to the individual at which an abnormal response to the milieu in which inadequate delivery of glucose to the target organ occurs.

Upward shift

- The definition for hypoglycaemia has progressively shifted:
  - <1.5 mmol/l (1959-69)
  - < 2.2 mmol/l (1970-87)
  - < 2.6 mmol/l* (1988-98)
  - < 3.2 mmol/l (since 1999 in USA)

*World Health Organisation recommends 2.6 mmol/L for infants at risk without abnormal signs*

*Most commonly used in Australia, NETSVIC Handbook*
Breastfeeding and blood glucose

Systematic review  37 – 42 week at birth
  – Type of feeds
  – Timing of feeds
  – Themoregulation

Studies did not adequately describe
  – effectiveness of monitoring
  – developmental outcomes
  – breastfeeding success.

Breastfeeding and blood glucose

• When initiated early
• associated with frequent sucking,
• provides
• adequate plasma glucose for the neonate in the first 48 hours of life, with no need for supplemental feeds or water in a healthy neonate

Skin – to - skin

Optimal for adaptation after birth helping to maintain
• body temperature
• and safe blood glucose levels

in the healthy term newborn infant

Breastfed Infants

- Have higher concentrations of ketone bodies than formula-fed infants
- Tolerate lower plasma glucose levels without any significant clinical manifestations or sequelae

*Patterns of metabolic adaptation for preterm and term infants in the first week*

Hypoglycaemia - diagnosis

3 criteria

- Clinical manifestations
- Co-incident low plasma glucose measured accurately
- Prompt resolution of clinical signs with treatment of hypoglycaemia

- (Whipple’s triad)
Measurement issues

• Blood sugar levels (BSL) vs true blood glucose (TBG)

• Reagent stick screening is not accurate at low levels.

• Sources of error
## BSL vs TBG

<table>
<thead>
<tr>
<th></th>
<th>BSL</th>
<th>TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>Glucometer / POC</td>
<td>Blood Gas machine</td>
</tr>
<tr>
<td>Place</td>
<td>Cotside</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Advantage</td>
<td>Quick</td>
<td>Slower / Accurate*</td>
</tr>
<tr>
<td>Disadvantage</td>
<td>Accuracy* ± 0.5 mmol/L</td>
<td>Second sample</td>
</tr>
</tbody>
</table>

* Major Issue
Sources of Error

**Sampling**

- Capillary sample must flow freely (haemolysis)
- Arterial levels > venous

**Haematocrit variation**

- (plasma glucose levels 18% higher than whole blood)
- Higher the haematocrit the lower the glucose level
Infants at risk - 1

Reduced glycogen stores or increased glucose demands

• Premature
• IUGR
• perinatal asphyxia
• Hypothermia
• RDS
• sepsis
Infants at risk - 2

Hyperinsulinaemic states

- Infants of diabetic mothers
- Rhesus isoimmunisation
- Beckwith-Weidemann syndrome

Rare Conditions

- Metabolic Aminoacidopathy
- Nesidioblastosis / Islet cell adenoma
Screening

Reserved for infants who may be at risk since hypoglycaemia in the normal healthy neonate is usually a transient condition that resolves itself without need for intervention*. 

Blood glucose

should not be measured too soon after birth when all newborn infants are likely to have low blood glucose#

When to test infants at risk?

- ? at birth
- ? 1 hour of age
- ? 2 hours of age
- ? 4 hours of age
- ? before or after a feed

Guidelines vary in the specifics.

Majority of hospital guidelines suggest first blood sugar is taken at 2 hours of age.
What to do?

Apply usual principles of care

• Keep mother and baby together
• Skin to skin
• Free access to the breast (if mother has made informed choice to breastfeed)
Breastfeeding and blood glucose in Infants of women with GDM

<table>
<thead>
<tr>
<th>Borderline TBG 1.93 – 2.48 mmol/L</th>
<th>n</th>
<th>Breastmilk</th>
<th>Formula</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 1.9 h</td>
<td>67</td>
<td>9% (4)</td>
<td>46% (11)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Glucose level

| Mean 1.9 h                       | 67| 3.2 ± 0.63 | 2.68 ± 0.58 | 0.002 |

“If the baby is unable to feed soon after birth and colostrum is unable to be expressed, the baby is likely to be fed artificial milk to ensure stable levels of blood sugar. Research has indicated that artificial milk contains bovine serum albumin which is associated with generating an autoimmune response. This autoimmune response has been associated with an increased risk of Type 1 DM for the infant particularly where there is also a family history of Type 1 DM. Antenatal expression of colostrum will allow storage of a small amount of colostrum which will reduce the use of artificial milk with babies at increased risk of Type 1 DM.”
Pilot: Diabetes and Antenatal Milk Expressing*

33 women with GDM expressed from 36 W

<table>
<thead>
<tr>
<th>Colostrum</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (mls)</td>
<td>35.5</td>
<td>5 - 181</td>
</tr>
<tr>
<td>Volume / expression (mls)</td>
<td>1.56</td>
<td>0.21 – 7.83</td>
</tr>
<tr>
<td>No. Days expressing</td>
<td>14</td>
<td>4 - 30</td>
</tr>
<tr>
<td>No. Expressing episodes</td>
<td>24</td>
<td>7 - 56</td>
</tr>
</tbody>
</table>

Infants: 10/33 admitted SCN
8 hypoglycaemia, TBG < 2.6 mmol/L
41% had formula in first 24 hours (MHW usual 59%)
At discharge 61% breastfeeding, 81% by 6 weeks age

DAME RCT in progress

- N= 658  RWH and MHW
- Women with diabetes in pregnancy
- Outcome is safety
- Recruited at 34 weeks gestation
- Randomised to express or not from 36 W
- Chief Investigator: Prof Della Forster
- Trial Coordinator: Anita Moorhead
- 3 year NHMRC funding
Infant of Diabetic Mother

- Macrosomia - 2 x fat of AGA infant,
- Organomegaly
- Hypoglycaemia
- Hypocalcaemia, hypomagnesemia
- Hyperbilirubinemia
- Hyperviscosity
- Respiratory Distress
- Cardiomyopathy - hypertrophic/congestive
- Persistent pulmonary hypertension
- Congenital anomalies
Perinatal Mortality in Diabetic Pregnancies
(Deaths per 1000 births)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Gestational Diabetes</th>
<th>Pre-existing</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal</td>
<td>4.7</td>
<td>10.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Perinatal</td>
<td>3.0</td>
<td>12.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Neonatal</td>
<td>8.0</td>
<td>22.6</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Californian data, 1986
# Congenital Malformations in Infants of Insulin Dependent Diabetic Mother

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Risk Ratio</th>
<th>% Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiac</td>
<td>18 x</td>
<td>8.5</td>
</tr>
<tr>
<td>All CNS</td>
<td>16 x</td>
<td>5.3</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>13 x</td>
<td></td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>20 x</td>
<td></td>
</tr>
<tr>
<td>All Anomalies</td>
<td>8 x</td>
<td>18.4</td>
</tr>
</tbody>
</table>

Congenital Anomalies in IDM

- Congenital heart disease – no specific
- Neural tube defects – full spectrum
- Renal agenesis
- Ureteral and urethral anomalies
- Small left colon syndrome
- Caudal regression syndrome
- Femoral hypoplasia-unusual facies syndrome
Fetal Effects

• Glycemic control during embryogenesis is critical

• Frequency of congenital anomalies proportional to level of maternal HbA1c

• No increase in birth defects in infants of mothers who develop diabetes after first trimester
Diabetic Pregnancy complications

- Pre-eclampsia
- Polyhydramnios
- Labour & Delivery complications
  - shoulder dystocia (↑ 2- 4x normal)
  - brachial plexus injury
  - asphyxia
- increased rate of caesarean section
- Perinatal mortality 2x non-diabetic
Abnormal Glucose Homeostasis - Infant of Diabetic Mother

- At risk of hypoglycaemia
- Increased muscle, fat and liver mass
- Transient hyperinsulinism leads to reduced:
  - Concentrations of free fatty acids and ketone bodies
  - Postnatal glucagon surge
Hypoglycaemia in IDM

• Occurs 1 - 5 hours after birth
• related to maternal control in 6-12 weeks prior to delivery, even 3 – 4 days prior is influential
• recommend early breast feeding
• monitor blood sugar levels
Hypoglycaemia - monitoring

- monitor blood sugar
- hypoglycaemia < 2.6 mmol/l
- ideally true blood glucose if glucometer level “low”
- confirm glucometer levels with TBG
- test pre feed
- frequency - initial by 2 hours of age
- suggest at least 3 successive normal readings before cessation
Hypoglycaemia - treatment

• Early oral feeds, preferably breast /EBM
• - if formula, not hypercaloric
• If hypoglycaemia persists despite good feed
  - Intravenous 10% Dextrose
  - Avoid rebound hyperglycaemia
  - Minibolus of 10% Dextrose 2 mls/kg only if profound hypoglycaemia
  - Continue some oral feeds
• Glucagon/Steroids/Diazoxide/Somatostatin may be used in refractory infants
### Infant Outcome – ACHOIS trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Routine Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>10%</td>
<td>21%</td>
</tr>
<tr>
<td>SGA</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Hypoglycaemia – IV Dextrose</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>RDS</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* *p < 0.001*

Crowther et al. NEJM. 2006. 352: 2477 - 2486
Childhood Effects

- Growth effects observed to continue into childhood

Silverman*, 1995, 8 year follow-up
- deranged glucose kinetics
- girls increased risk gestational diabetes

Supporting breastfeeding

For the mother whose infant is at risk of hypoglycaemia

• Antenatal awareness
• Educate mother about skin – to - skin
• Early, frequent proximity to breast

If baby does require treatment consider impact of how that is delivered.
Academy of Breastfeeding Medicine

Clinical Protocol #1:

Guidelines for Glucose Monitoring and Treatment of Hypoglycemia in Breastfed Neonates

Revision 2006

Bibliography: 39 references

www.bfmed.org
ABM protocol.

Early and exclusive breastfeeding meets the nutritional and metabolic needs of healthy, term newborn infants.

• 1. Routine supplementation is unnecessary.
• 2. Initiate breastfeeding within 30 to 60 minutes of life and continue on demand.
• 3. Facilitate skin-to-skin contact of mother and infant.
• 4. Feedings should be frequent; 10 to 12 times per 24 hours in the first few days after birth.
Glucose screening is performed only on at-risk or symptomatic infants.

1. Routine monitoring of blood glucose in all term newborns is unnecessary and may be harmful.

2. An at-risk infant should be screened for hypoglycemia with a frequency and duration related to the specific risk factors of the individual infant.

3. Monitoring continues until normal, preprandial levels are consistently obtained.

4. Bedside glucose screening tests must be confirmed by formal laboratory testing.
Asymptomatic Infant

1. Continue breastfeeding (approximately every 1 to 2 hours) or feed 3 to 10 mL/kg of expressed breast milk or substitute nutrition.
2. Recheck blood glucose concentration before subsequent feedings until the value is acceptable and stable.
3. Avoid forced feedings.
4. If glucose remains low despite feedings, begin intravenous glucose therapy.
5. Breastfeeding may continue during IV glucose therapy.
Symptomatic Infant

Or infants with plasma glucose levels 1.1 to 1.4 mmol/L

1. Initiate intravenous 10% glucose solution.
2. Do not rely on oral or intragastric feeding to correct extreme or symptomatic hypoglycemia.
3. The glucose concentration in symptomatic infants should be maintained 45 mg/dL (2.5 mmol/L).
4. Adjust intravenous rate by blood glucose concentration.
5. Encourage frequent breastfeeding.
6. Monitor glucose concentrations before feedings as the IV is weaned until values stabilize off intravenous fluids.
Learning Objectives

• Understand glucose physiology and biochemistry
• Know symptoms of hypoglycaemia
• Definition and evidence
• Measurement and screening
• Infant of the diabetic mother (IDM)
• ABM protocol