Screening babies with Hypoglycaemia – finding the right needles in the right haystacks.

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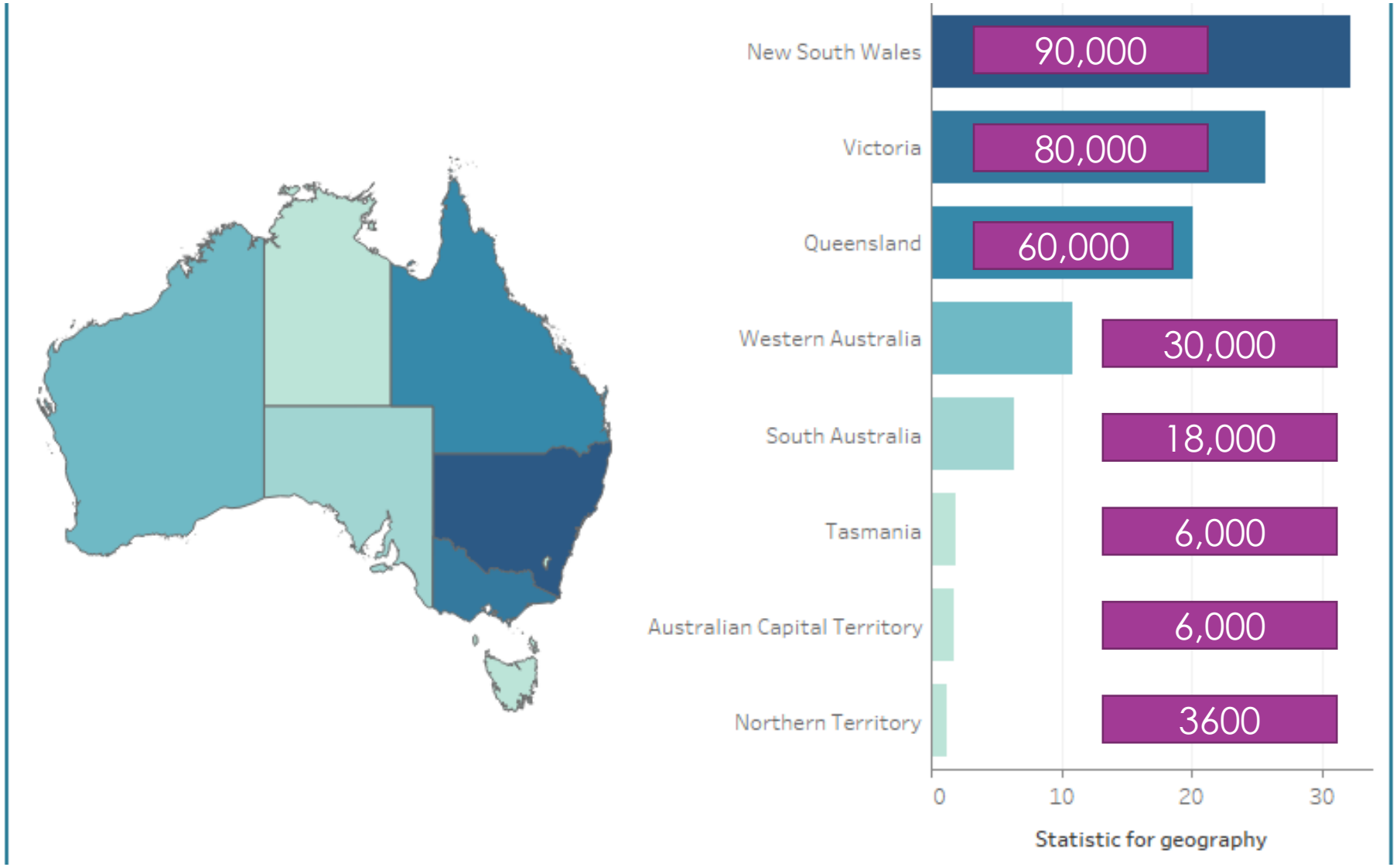
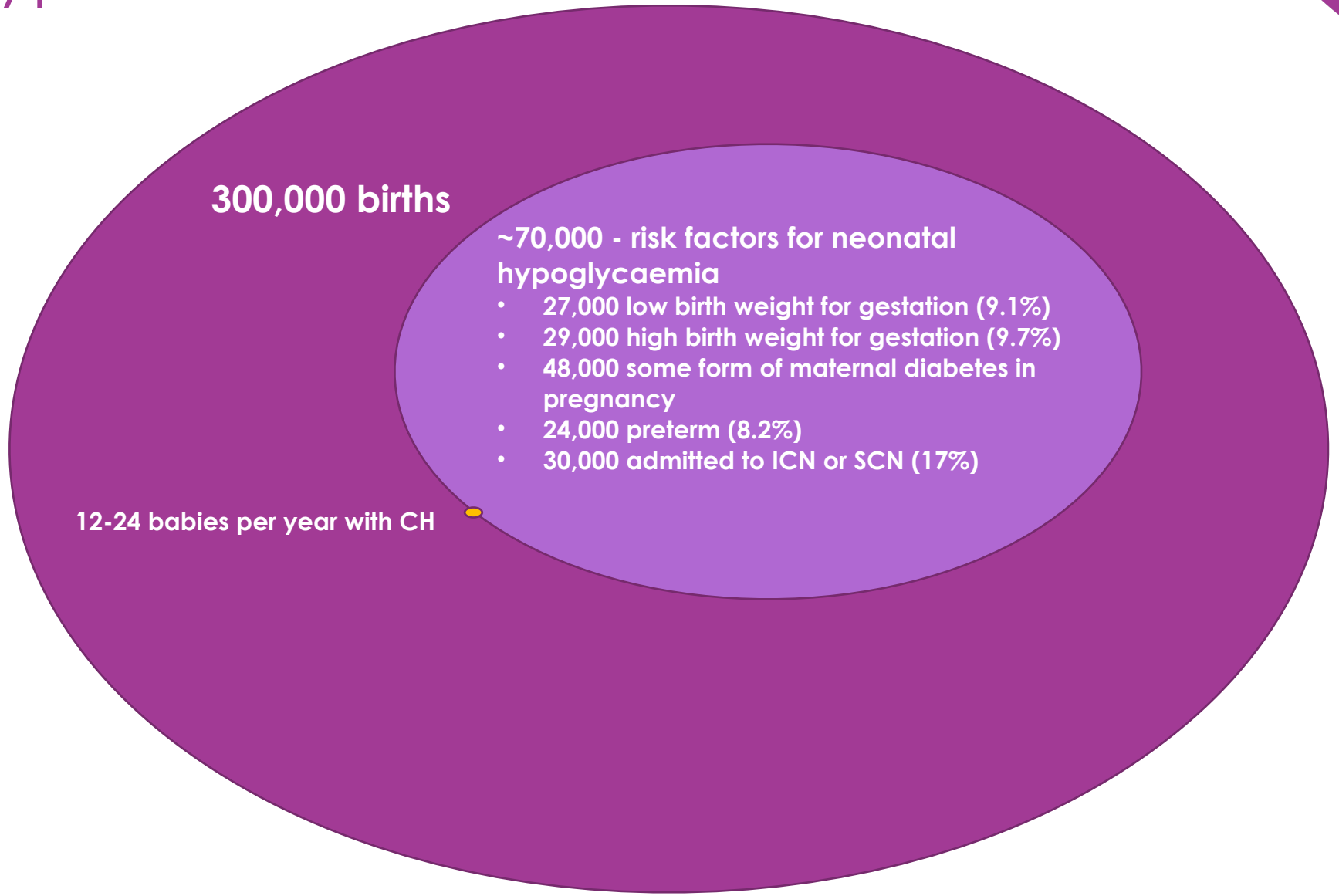
Births in Australia - ~300,000/year



AIHW Mothers and Babies 2021

Trying to find congenital hyperinsulinism



Maternal glucose control in normal pregnancy

- First half of pregnancy – maternal basal insulin secretion relatively normal
- Second half of pregnancy
  - Insulin secretion exaggerated (3x production in non-pregnant state)
  - Insulin antagonised by human placental lactogen, oestrogen, progesterone
  - Insulin clearance may increase, binding is normal
  - **Insulin sensitivity 40-60% of non pregnant state.**
- Effect is to
  - **Meet glucose and nitrogen needs of the growing fetus**
  - **Protect the fetus against reduced substrate delivery during maternal fasting**
  - **Maternal blood glucose levels sustained, or, when maternal hypoglycaemia eventually ensues…..**
  - **Maternal ketogenesis promoted (fetal brain can use ketones from 10-12 weeks).**

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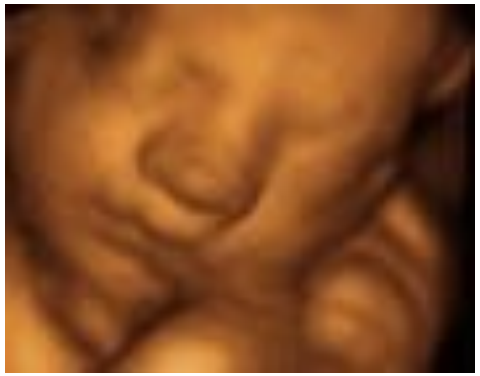
Neonatal glucose balance – why is there a problem?

In the fetus

- glucose from the mother at ~ 5 mg/kg/min
- amino acids from mother and lactate from placenta are also important sources of energy
- Fetus undertakes little or no gluconeogenesis
- Insulin and glucose stimulate accumulation of glycogen and fat to support extra-uterine life (high insulin/glucagon ratio)
- Near term – glucocorticoids contribute to glycogen deposition



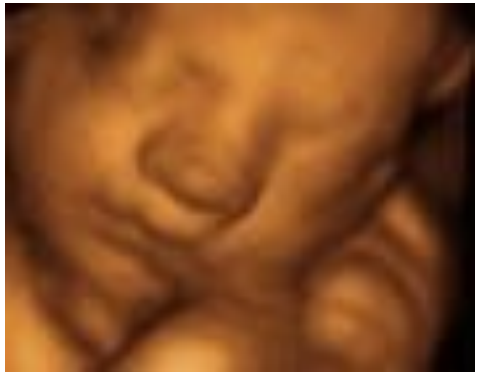
In the newborn

- Rapid switch needed from continuous glucose supply via the placenta to intermittent nutrient supply via the gut
- Brain needs ~ 3.7 mg/kg/min glucose continuously

Transition – abrupt changes

Fetus

- Continuous glucose supply via placenta
- High carbohydrate, low fat diet
- **Two systems required for success:**
  - A functioning placenta
  - A functioning fetal pancreas that can make insulin



Newborn

- Intermittent supply via the gut
- High fat, low carbohydrate diet
- **Seven systems required for success:**
  - Successful feeding
  - Liver that can break down glycogen
  - Liver that can make glucose from other molecules (lactate, alanine, glutamine)
  - Adipose tissue lipolysis
  - Fatty acid oxidation and hepatic ketogenesis
  - Normally functioning fetal pancreas (can switch insulin production on and off)
  - Hormonal regulation of these systems

Normal physiology

- First hours of postnatal life – transition from continuous glucose across the placenta, to intermittent supply from milk feeds
- Insulin falls and catecholamines and glucagon are released
- Essential enzymes for production of glucose from glycogen, body fat ketones switched on (unless inhibited by persistent insulin)
- Stimulation of appetite and promotion of fat metabolism from fat stores and milk feeds

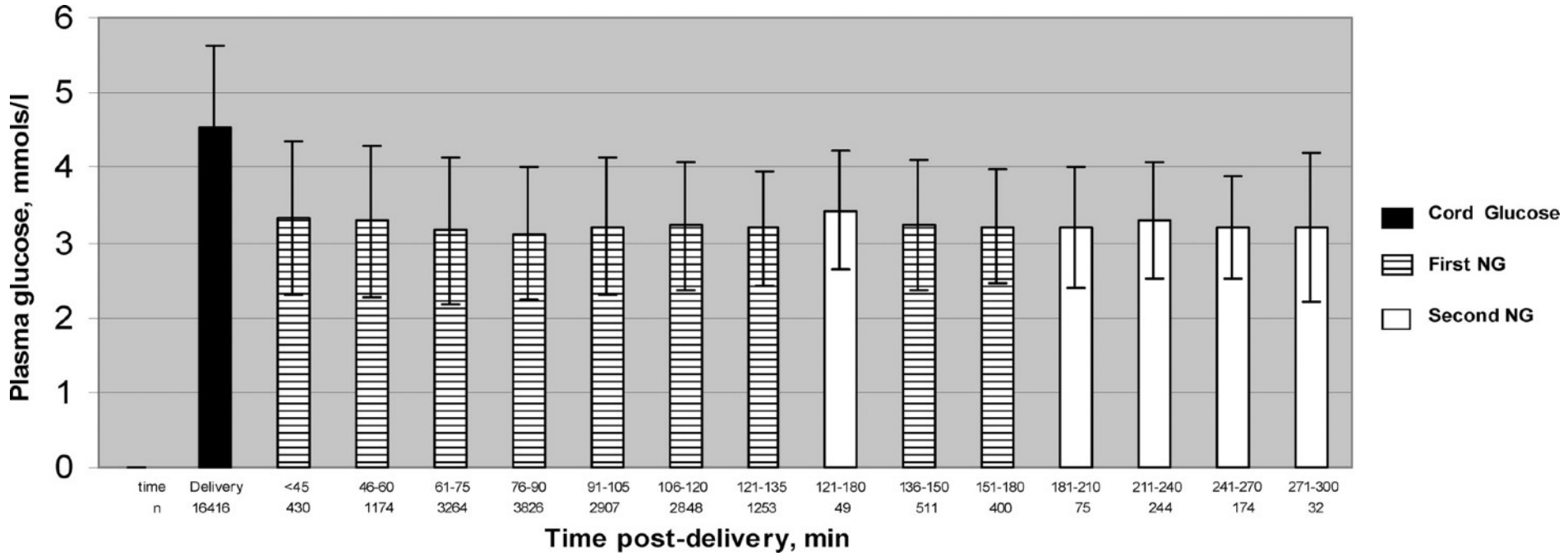
Why and when do we encounter problems?

1. **Various forms of maternal diabetes:** Maternal hyperglycaemia -> fetal hyperglycaemia -> fetal islet cell hyperplasia -> neonatal hypoglycaemia (Pedersen hypothesis – 1920s)
2. **Delay in normal perinatal transition**
3. **Low glycogen stores plus delay in feeding**
4. **Inborn errors of metabolism**
5. **Congenital endocrine disorders:**
   - Persistent hyperinsulinaemic disorders
   - Hypothalamic or hypopituitary conditions
   - Adrenal conditions
6. **Increased metabolic rate** (usually stress mechanisms compensate)

Neonatal blood sugar levels

- BGL is low in the first six hours of life.
- Lack of international consensus about the normal range for pre-feed plasma glucose in the normal healthy baby during this time period.
- The blood glucose usually
  - falls in the first two to four hours of life then,
  - by four to six hours of age stabilises at 2.5–4.4 mmol/L (may be up to 6.2 mmol/L)
  - Over subsequent days the mean BGL rises slowly to concentrations seen in older children and is generally acceptable if >3 mmol/L by 3rd day, 3.5 mmol/L by 4th day without any treatment in place

Temporal patterns of cord plasma glucose and neonatal plasma glucose (NG) concentrations
Figure shows mean ± SD.



Boyd E. Metzger et al. Pediatrics 2010;126:e1545-e1552

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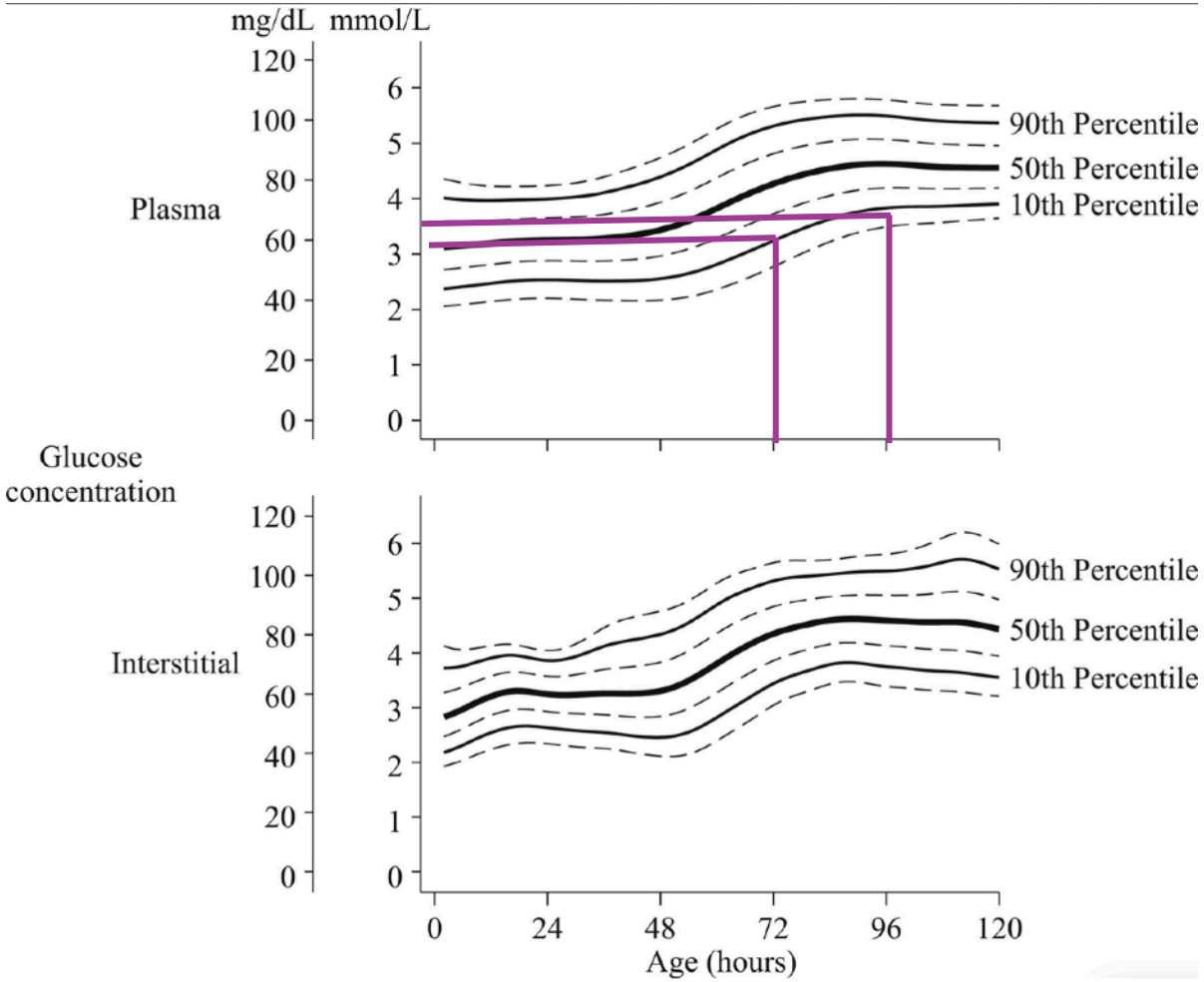
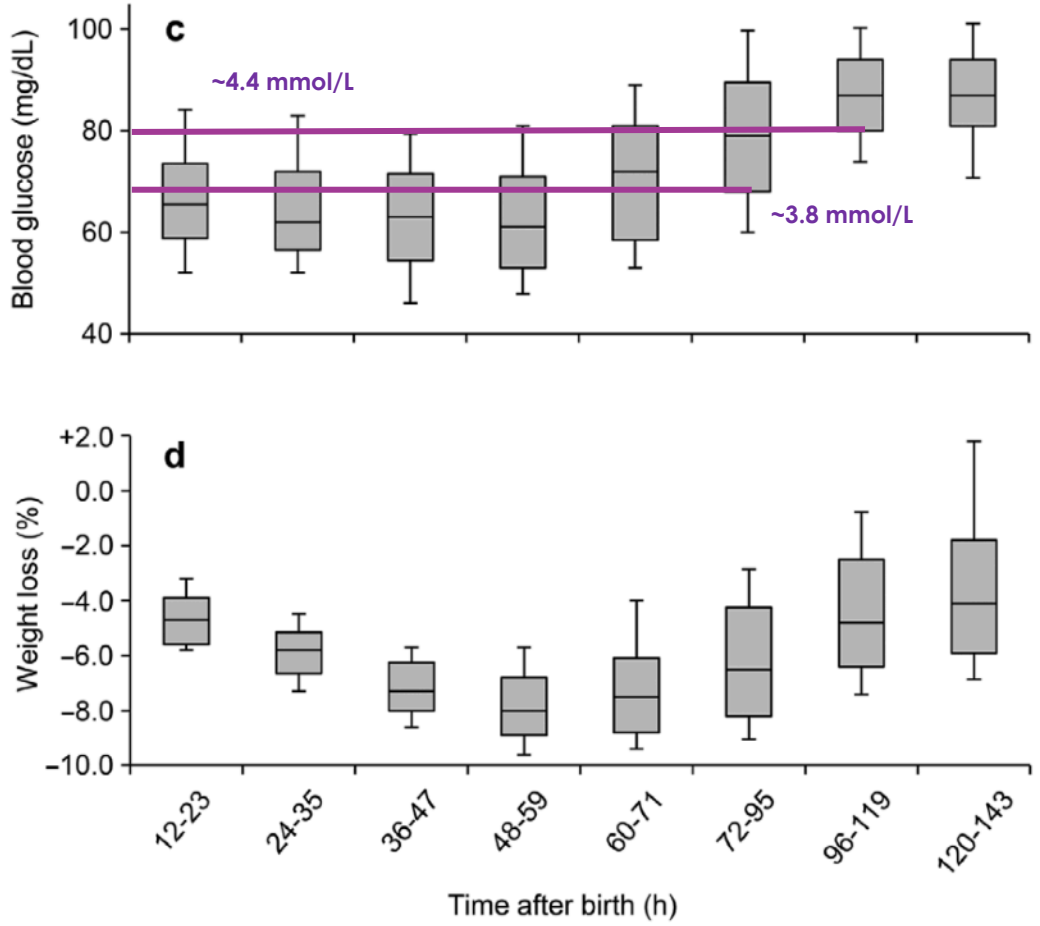
Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW) Study J Pediatr. 2020 Aug;223:34-41





Futatani T, Ina S, Shimao A, Higashiyama H, Fujita S, Igarashi N, Hatasaki K. Exclusive breast-feeding and postnatal changes in blood sodium, ketone, and glucose levels. Pediatr Int. 2019;61(5):471-474

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Queensland Neonatal Hypoglycaemia Guidelines

Queensland Clinical Guidelines
Translating evidence into best clinical practice

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Maternity and Neonatal **Clinical Guideline**

Hypoglycaemia–newborn

- Updated September 2019
- Update commenced 2023
- Clinical leads – Helen Liley, Karen Hose
- Large working party, specific expert advice from
  - Professors Jane Harding and Louise Conwell

QH Guidelines update

- Encouragement to avoid mother-infant separation and interruption of breast feeding/breast milk feeding where possible
  - Avoid hypothermia/cold stress
  - Early feeding
  - Glucogel – emphasis that this is to improve the quality of the immediately subsequent feed, not to "treat" the hypoglycaemia
- If above measures insufficient, discussion with mother about potential advantages of complementary formula feeds vs IV therapy
  - Brief exposure to intragastric formula feeds in hospital – low risk of affecting:
    - Establishment of breast feeding
    - Gut microbiome

QH Guidelines update

- Description of mechanisms of hypoglycaemia in the newborn – one or more of
  - Increased levels of insulin
  - Increased glucose utilisation
  - Inadequate glucose supply
  - Inadequate body stores (glycogen, fat)
  - Decreased levels of counter-regulatory hormones (e.g., growth hormones, cortisol, adrenergic hormones)
  - Disorders of glycogen metabolism (glycogenolysis)
  - Disorders of glucose production (gluconeogenesis)
  - Congenital anomalies, or unknown or mixed causes

QH Guidelines update - continued

- Maternal risk factors
  - Maternal medications – including beta blockers, betamethasone
  - Maternal diabetes
  - Family history of genetic conditions
  - Intrapartum IV glucose (>20 g/hour – e.g., Hartmann's at >400 mL/h or glucose 10% >200 mL/h)
  - Pre-eclampsia
- Neonatal risk factors for the conditions in the previous slide
- Guidelines for which babies should have screening and definition of how and when to screen

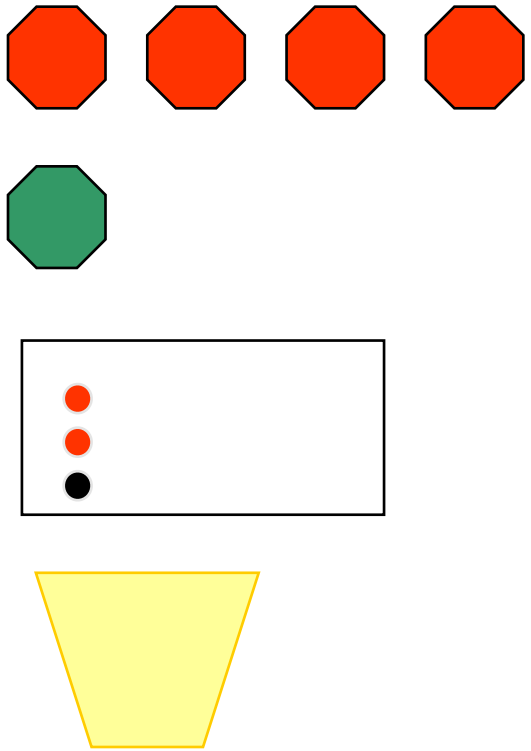
QH Guidelines update – When IV therapy needed

- Try to avoid complete cessation of feeds except when essential
- Maintain awareness of the Glucose Infusion Rate

Glucose mg/kg/minute				
	mL/kg/day			
%	60	80	100	120
10%	4.2	5.6	6.9	8.3
12%	5	6.7	8.3	10
14%	5.8	7.8	9.7	11.7
16%	6.7	8.9	11.1	13.3
18%	7.5	10	12.5	15
20%	8.3	11	13.9	16.7

- Use glucose boluses with caution(risk of rebound and rapid swings in BGL may be harmful)

Investigations of babies with hypoglycaemia
(while blood glucose <2.6 mmol/L)



2-4 red top micro tubes

1/2 green top on ice

1-2 spots on screening card (for acyl carnitine)

Urine sample (Metabolic screen)

Total is about 2 mL blood, plus urine sample

- Glucose, lactate, ammonia
- Insulin, growth hormone, cortisol
- β OH butyrate, free fatty acids
- Acylcarnitine profile
- Urine metabolic screen (urine amino & organic acids)
- Haematocrit or Full blood count if indicated

QH Guidelines update - continued

- When to perform a "Hypo screen" (severe, symptomatic, persistent/ recurrent hypoglycaemia) and how to do it
  - Prioritisation of tests if insufficient sample
- Clearer description of pharmacologic therapy – which drugs, how to give them, adverse effects
- Clarification of who needs a 6-hour fast before discharge, and how to do it.
- Improved parent information

Thanks!

…questions?