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Glucose in Well Babies Steering Committee

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## Version record

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| Date | Version | Updates |
| 20 June 2015 | V. 1 | Working copy for funding and registration applications |
| 3 September 2015 | V. 2 | Changes included  Eligibility criteria to exclude multiples  Growth charts changed from the International INTERGROWTH charts1 to The Australian Fenton Charts2 |

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# Glucose in Well Babies Study - GLOW

## Project Summary

Neonatal hypoglycaemia is important because it is common and linked with brain injury and poor neurological outcome. In recent years, there has been considerable interest in the detection and management of neonatal hypoglycaemia. Babies who are identified as being at risk are screened using heel-prick blood tests for the first days after birth. If hypoglycaemia is diagnosed, then treatment is usually provided. Glucose is the primary cerebral fuel and the aim of treatment is to increase the blood glucose concentration to ensure adequate cerebral energy supply.

The definition of neonatal hypoglycaemia has caused considerable controversy. The current widely accepted definition of < 2.6mM has been determined using limited, but the only available data. However, the normal glucose profile of healthy appropriately grown term newborns has never been reliably described, and it is possible that many babies are being unnecessarily treated. Babies have been shown to use alternative cerebral fuels, primarily lactate and ketones, but the profiles of blood lactate and ketone concentrations in healthy newborns within the first week are also unclear.

We propose a prospective observational cohort study in healthy appropriately grown term newborns to describe the normal glucose, lactate and ketone concentration profiles over the first five postnatal days. Babies enrolled in the study will be cared for as normal newborns, largely by the parents as they progress from hospital or birthing centre to home.

Blood samples for analysis of glucose, lactate and ketones will be taken initially from the umbilical artery. Capillary blood tests will then be taken by heel pricks, initially matching the frequency of blood tests taken according current screening protocols for babies born at risk of neonatal hypoglycaemia, and continue for the first five postnatal days. In addition, all babies will have continuous interstitial glucose monitoring. The results of the blood and interstitial glucose measurements will not be available to clinicians caring for the baby.

If “neonatal hypoglycaemia” as currently defined is shown to be common in healthy term newborns, it is possible that current clinical management of babies at risk will significantly change.

## Aims

### Research outcome

To describe the blood glucose, lactate and ketone concentration profiles in term, healthy, appropriately grown babies in the first five postnatal days.

### Specific aims

To determine

* the incidence of blood glucose concentrations < 2.6mM
* the range and variation of blood and interstitial glucose concentrations
* the range and variation of blood lactate and ketone concentrations
* the differences, if any, between breast-fed and formula fed babies in blood glucose, lactate and ketone concentrations.

## Background and rationale

Neonatal hypoglycaemia is important because it is common and linked with brain injury and neurodevelopmental delay.3, 4 The severity, frequency and duration of hypoglycaemia required to cause brain injury remains unclear.5 However, blood glucose concentrations < 2.6mM have been linked with impaired brain function and neurodevelopmental delay.6, 7 In recent years there has been considerable research into the detection and treatment of babies at risk of hypoglycaemia. Screening for low blood glucose concentrations using intermittent heel-pricks is recommended for babies identified as being at-risk.8, 9 Of babies at risk, half will become hypoglycaemic within the first 48 hours after birth.10 However, there is no reliable evidence describing the normal blood glucose profile in the first week after birth.5

Older reports have shown that blood glucose concentrations in newborn babies fall immediately after birth, reaching a nadir between 30 and 90 minutes.11-13 Following the nadir, regardless of feeding, the blood glucose concentration increases and stabilises by between 12 to 48 hours, reaching concentrations consistent with adult glucose concentrations between days 3 and 4.13 However, applying these findings from older studies to the current clinical care for newborns is difficult, for two key reasons. Firstly, previous studies have excluded exclusively breast fed babies.14 Secondly, healthy babies used to remain in hospital for up to a week after birth and the nursery protocols, rather than the baby, directed the feeding regimens. Current recommendations for newborn care differ considerably from those approaches. Mothers and babies are encouraged to establish skin-to-skin contact and breast-feeding as soon as possible after birth,15 babies are encouraged to feed frequently, and remain in hospital only if healthcare treatment is required.

Reports regarding glucose concentrations in healthy newborns are few. Comparison between studies is difficult as some studies are cross sectional,16, 17 others longitudinal,12, 18 and one study used both methods.11 Furthermore, all reports have used differing feeding regimes.11, 12, 14, 17-19 Importantly, all previous studies have used intermittent blood glucose measurements, sampled at varying intervals between 1 and 24 hourly.11, 12, 16-18 Thus, changes in blood glucose concentrations between sampling are not captured. Hence, the current descriptions of normal glucose profiles provide only a ‘snap shot’ and the longitudinal profile remains undescribed.

We have developed considerable experience using continuous glucose monitoring in babies at risk of neonatal hypoglycaemia.20, 21 Continuous glucose monitoring is safe and reliable in at-risk babies and provides the opportunity to measure the continuous relationship between glucose concentrations and feeding even in the most fragile extremely preterm babies.22 There have been no reports that we are aware of using continuous glucose monitoring in healthy term newborn babies. A recent report has highlighted the need for continuous glucose monitoring data in healthy babies.23

### Blood glucose screening

Blood glucose screening is standard practice for babies identified as being at risk of hypoglycaemia, and is most commonly performed before feeding using heel-prick sampling. The screening recommendations are based on limited but the best available evidence in at-risk babies.8, 9 In most Australasian nurseries, babies at risk of hypoglycaemia are required to have three pre-feed blood glucose concentrations ≥ 2.6mM at least three hours apart, before screening is discontinued.

We are unaware of any data describing blood glucose concentrations in healthy term babies at the time that at-risk babies are screened. However, there have been repeated calls from high-level research5 and professional groups24 identifying an urgent need for these data. There may be very little difference in the measured glucose concentration between healthy term babies and those identified as being at risk for neonatal hypoglycaemia. Furthermore, there is no evidence that treating transitional hypoglycaemia improves neurological outcome in at-risk babies.5 If the blood glucose concentrations are similar in babies at risk, and those not at risk, this may lead to a considerable change in the management of newborn babies in relation to hypoglycaemia.

The definition of neonatal hypoglycaemia has caused considerable controversy, and the clinical significance hypoglycaemia remains unclear.5 At-risk babies with a blood glucose concentration < 2.6mM are usually treated, with the aim of treatment being to reduce the risk of neurological impairment. Yet limited data show that low blood glucose concentrations do occur in healthy term babies within the first week after birth. Authors from two cross-sectional studies have suggested the incidence to be as high as 14 %16, 17, which is likely to be an underestimate due to the intermittent nature of blood glucose sampling. There are no data about the frequency, severity, and duration of low blood glucose concentrations in healthy newborns.

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### Alternative cerebral fuels

Glucose is the primary metabolic fuel for cerebral oxidation. However, babies are known to use alternative cerebral fuels, primarily lactate and ketones. There is a paucity of data about these fuels in newborn babies16, and even fewer reports in healthy babies. Consequently, the relationship between these fuels and cerebral function remains unclear. However, there is increasing clinical interest in alternative cerebral fuels25, including a recent recommendation that the blood concentrations of ketone should be measured during neonatal hypoglycaemia.26 Therefore, there is an urgent need to describe the normal blood ketone and lactate concentrations in healthy newborns.

One of the reasons for the lack of data is that until recently, it has been impossible to accurately measure blood glucose, lactate, and ketone concentrations simultaneously using a small amount of blood. However, we now have the ability to measure glucose, lactate and ketones using 0.1ml of blood. Therefore we have an opportunity to measure and describe the normal concentrations and variations in healthy newborns.

### Feeding

Feeding appears to be the most effective way of preventing hypoglycaemia. Historical reports have shown that prolonged fasting in babies is linked with a progressive fall in blood glucose concentration.27 Breast feeding is encouraged and recommended for both mother and baby. A small number of studies have shown the type of milk a baby receives may influence the blood concentrations of glucose and ketones, with some reports showing that breast fed babies have lower blood glucose concentrations than formula fed babies28, 29, and others show the opposite.12

The original cross-sectional study reported by Hawdon16 included healthy term newborns within the first week after birth and showed that breast-fed babies (n =71) had lower blood glucose and higher ketone concentrations over the first four days, when compared with formula feed babies (n= 61). These data have been used to suggest that breast fed babies are protected from the risk of neurological damage because of the increased availability of ketones when compared to formula fed babies. Yet, we have shown in a cohort born 2010 - 2012 that hypoglycaemic newborns have low concentrations of ketones in the first 48 hours.30, 31 Therefore there is an urgent need to determine normal concentrations of lactate and ketones in the context of current feeding recommendations, using a more robust research method.

We propose a prospective observational cohort study in healthy term appropriately grown newborns. We will describe the normal blood glucose, lactate and ketone concentrations, using standard blood testing and also continuous interstitial glucose monitoring from soon after birth to the completion of five postnatal days, while also capturing information about feeding.

## Research Plan

### Study design

Prospective observational cohort study

### Study Setting

It is expected that most babies will be in their own homes for much of the duration of the study. However, babies may start the study at Waikato Women’s Hospital or a primary birthing centre.

### Study population

#### Inclusion criteria

* Singletons
* 37 to 42 completed weeks’ gestation
* Appropriate weight for gestation age (birthweight ≥ 10th centile and ≤ 90th centile).2
* Living within 20 kilometres of Waikato Hospital
* English-speaking parents

#### Exclusion criteria

* Birthweight < 2500 g or > 4500 g
* Apgar score < 7 at five minutes of age
* Skin conditions preventing the attachment of the continuous glucose monitor.
* Unwell for any reason
* Major congenital abnormalities
* Terminal conditions
* Born to mothers with an antenatal history of diabetes, drug dependency, or using medications that may affect the baby’s blood glucose concentration, e.g. corticosteroids, sodium valproate.
* Born to mothers with a Body Mass Index < 18.5 or > 30 kg/m2 32

## Recruitment

### Informed Consent

All parents identified before birth as expecting a healthy baby will be provided with an information pamphlet in antenatal areas, midwifery clinics or delivery suite. After discussion with a member of the research team, written informed consent will be sought. A copy of the consent form will be kept with the mother’s midwifery notes and the Lead Maternity Care provider will also receive a letter that will provide details about the study. In addition, consented families will be given information about how to contact a member of the research team prior to the birth of the baby. Babies will be enrolled in the study once eligibility is confirmed immediately after birth.

### Withdrawal from the Study

Parents will be able to discontinue participation in the study at any time. It is expected that some families will withdraw from the study prior the completion of five days. If parents do choose to withdraw, we will seek permission to include all data collected in analysis. If parents do not want their data to be included in the analysis, all data will be returned to the family.

## Study Procedures (Appendix 1)

### Daily plan and review

Following the birth of an eligible baby, each family will receive an individual plan, which will outline the time frames in which the research staff will be visiting the baby to perform the blood tests and daily review. A member of the research team will be on call for the parents at all times.

In the unlikely event of a baby becoming unwell for any reason, the Lead Maternity Carer will be notified and organise any required referral. Any required investigations, including blood samples, will be taken as clinically indicated, independent of the study protocol, and the baby will remain in the study, unless the parents request otherwise.

### Blood glucose, lactate and beta-hydroxybutyrate analysis

Blood glucose and lactate samples will be analysed using glucose oxidase and lactate oxidase on the portable epoc® analyser (Epocal Inc. Ottawa, Canada). Beta-hydroxybutyrate will be analysed using beta-hydroxybutyrate dehydrogenase on the hand held StatStrip™ meter (Nova Biomedical, Waltham, MA, USA).

The results screen of both analysers will be covered so that the researcher taking the blood sample will be unaware of the results.

### Sampling and Timing of the blood samples

Day 1

The first blood sample (0.1 ml) will be taken from the umbilical artery immediately after birth. One to two hours following birth, in accordance with the blood glucose screening protocol for at-risk babies at Waikato Hospital, the first heel-prick blood sample will be taken (0.1ml) and will be followed by 3 pre-feed heel-prick samples, at least three to four hours apart.10

Days 2 to 5

Heel-prick blood samples will be measured every 10 to 12 hours. It is standard practice for blood to be collected for the Newborn Screening Card on Day 3 after birth. Every attempt will be made to take one of the study blood samples at the same time.

An experienced neonatal nurse will warm the baby’s heel prior to each sample being taken to aid blood flow. In addition, each blood test will be taken just as a feed is being initiated, in order to reduce the pain and discomfort.33 There will be a maximum of 16 heel-prick blood tests and 1.6 ml of blood sampled over the five days.

### Continuous interstitial glucose monitor

As soon after birth as possible an Ipro2 continuous glucose monitor (Medtronic, Minimed®, Northridge, USA) will be inserted subcutaneously into the baby’s thigh using the insertion device and remain in place for five days. The sensor will be secured with a transparent dressing.

A RemoveTM(Smith & Nephew, Inc., St Petersburg, USA) wipe will be used to remove the dressing and sensor at the end of the study, in order to decrease the potential discomfort of removing the dressing. Following removal of the continuous glucose sensor the skin underneath the sensor will be assessed and cleaned. In the event of the sensor becoming dislodged, we will ask the parents if the sensor can be replaced. If the sensor requires replacement, an addition heel-prick blood test will be required 1 to 2 hours after the insertion of the new sensor.

### Feeding data

Parents will be encouraged to enter details of all feeds (breast or bottle) into a commonly used breastfeeding software application (Feed Baby Pro, Penguin Apps, Version 21.0.5, Victoria, Australia) on a small hand held computer device. At the completion of the five-day study period, data will be exported as a CVS file and stored in a secure database for later analysis. If the parents wish to have a copy of the feeding data in order to continue using the application on a personal device, we will email this information to them.

### Health information data

#### Maternal data

Demographic details regarding the mothers’ health, previous obstetric history and current pregnancy will be collected from the mothers’ clinical records.

#### Neonatal data

Demographic details about the birth, and weight, length and head circumference will be collected soon after birth and at the end of the study.

### Follow up

Both parents will be invited independently to complete a short questionnaire about their experience of the study within one week after the completion of the study. The questionnaire will be left for each of the parents at the end of the study. A member of the research team will collect both questionnaires, within the following week.

### Adverse events

All adverse events or concerns will be reported to the Steering Committee

#### Adverse event

1. Redness or swelling at the insertion site of the continuous glucose monitor.
2. Baby becoming unwell and requiring medical attention.

### Power and Sample size

Approximately 5,800 babies are born within the Waikato region each year. Of these babies 30 % are likely to be at risk of hypoglycaemia and therefore excluded from our possible study population, leaving approximately 4060 babies.

The Sugar Babies Study was performed at Waikato Hospital and surrounding Birthing Centres and achieved a 59 % recruitment rate (588/1002). While the population for the GLOW study differs, discussions with both parent groups and Waikato health services about the GLOW study have been supportive of the study.

Our first aim is to determine the incidence of neonatal hypoglycaemia within the first 48 hours, using the current definition of < 2.6mM. In the CHYLD Study the incidence of hypoglycaemia in term babies born at risk was 56% (240/258). In the healthy newborn population the incidence of hypoglycaemia is reported to be 15%16. Using a two-tailed design with alpha at 0.05 and beta at 0.2 we will therefore need 19 babies to demonstrate that the incidence of hypoglycaemia in term healthy babies is significantly lower than in term babies born at risk.

However, our major aim is to reliably describe the range and variation of blood glucose concentrations in healthy term babies within the first five postnatal days. The 258 term babies within the CHYLD study had mean glucose concentrations at 12 hours of age of 3.3mM (SD 0.7). In order to have a 95% level of confidence to detect the mean blood glucose concentration to a precision equivalent to a standard error of 0.17mM, we would need to recruit 50 babies.

However, we expect some families not to complete the study, so allowing for a 25 % withdrawal rate we will need to recruit 63 babies.

### Data Analysis

Categorical variables will be analysed using number and percent. Continuous variables will be analysed to determine the distribution, range, and variance.

Interstitial glucose concentration profiles will be recalibrated 34, examined for episodes of hypoglycaemia, and quantified for frequency, duration, and severity.20 Feeding data will be time matched with the interstitial glucose profiles and examined for feed-related variation using regression analysis, box plots and area under the curve analyses.

Our secondary analysis will include comparing the GLOW glucose and feeding data with data from subgroups of at risk babies (late, preterm, infants of diabetic mothers, small or large for gestation age) previously obtained from the Babies and Sugar Babies studies.20, 21 Data with repeated points, including blood glucose, lactate and ketone concentrations will be compared between babies and within babies, using a mixed model approach. Continuous data will be compared by Student’s t test or the Mann-Whitney U test if the data are not normally distributed and cannot be converted to near-normality by simple transformation. Prior to analysis commencing a statistical analysis plan will be completed.

### Data security

Healthcare professionals involved in the care of pregnant women will identify eligible families. All data collected including NHI number, expected date of delivery, entry criteria meet, and the signed consent form will be held by the principal investigator in a locked office or on a password protected computer. All data collected about families whose babies are not ultimately recruited to the study will be destroyed, although signed consent forms will be retained.

Access to health information collected during the study will be limited to recruitment staff. A secure database will hold any identifiable data separately from the trial data and access to this will be limited to the investigators. Only a study number will identify all study data.

Research data and all study records will be retained for 10 years after the age of majority.

### Significance

Presently, there is no reliable description of the normal glucose, lactate and ketone profiles in the first week after birth in healthy, term babies cared for according to contemporary practice. However, babies identified as being at risk for hypoglycaemia soon after birth, most of whom are otherwise healthy, are usually treated for hypoglycaemia if the blood glucose concentration is < 2.6mM. Furthermore, there is no evidence that treating transitional neonatal hypoglycaemia improves the neurological outcome for children or adolescents.5, 35

If this study shows that low blood glucose concentrations are common in healthy term babies, it is possible that the current management of neonatal hypoglycaemia will alter considerably, as fewer babies may be screened and treated for hypoglycaemia. This will have significant implications for babies, their families and health care resources.

### Project Management

#### Steering Committee

Dr Deborah Harris (Chair)

Dr Phil Weston

Distinguished Professor Jane Harding

#### Duties of the Steering Committee

The Steering Committee will take overall responsibility for all aspects of the study.

### Trial Duration

Recruitment is expected to commence in October 2015 and is expected to take one year.

### Ethics

The Northern A Health and Disability Ethics Committee approved the GLOW study on the 19 August 2015 (Number:15/NTA/104)

### Funding

The Waikato Sick Babies Trust has provided funding for the purchase of the portable epoc® analyser (Epocal Inc. Ottawa. Canada).

Waikato Medical Research Foundation have provided funds $30,060.00 which will allow for GLOW to commence.

### Trial Registration

The study will be registered with the Australian and New Zealand Clinical trials Registry (ANZCTR) before recruitment begins.

### Dissemination of results

Findings will be presented at local research and community meetings. We will also present findings at both at national and international meetings and publish in international medical journals.

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Appendix 1: Procedures for babies participating in GLOW

