Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW) Study

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Objectives To determine postnatal changes in plasma and interstitial glucose concentrations of healthy infants receiving current recommended care and to compare the incidence of low concentrations with recommended thresholds for treatment of at-risk infants.

Study design A prospective masked observational study in Hamilton, New Zealand. Healthy, term, appropriately grown singletons had continuous glucose monitoring and repeated heel-prick plasma glucose measurements (4 in the first 24 hours then twice daily using the glucose oxidase method) from birth to 120 hours.

Results The 67 infants had a mean birth weight of 3584 ± 349 g, and gestational age of 40.1 ± 1.2 weeks. The mean glucose concentrations increased over the first 18 hours, remained stable to 48 hours (59 ± 11 mg/dL; 3.3 ± 0.6 mmol/L)] before increasing to a new plateau by the fourth day (89 ± 13 mg/dL; 4.6 ± 0.7 mmol/L). Plasma glucose concentrations of 47 mg/dL (2.6 mmol/L) approximated the 10th percentile in the first 48 hours, and 39% of infants had ≥1 episode below this threshold. Early term infants had lower mean glucose concentrations than those born at later gestational ages and were more likely to have episodes <47 mg/dL (<2.6 mmol/L) (19/32 [59%] vs 7/35 [20%]; relative risk, 3.0; 95% CI, 1.4-6.1; P = .001).

Conclusions Healthy infants seem to complete their metabolic transition by day 4. Many have glucose concentrations below the accepted thresholds for treatment of hypoglycemia. *(J Pediatr 2020;223:34-41)*.

Trial registration ACTRN: 12615000986572.

See editorial, p 10

Glucose concentrations change rapidly after birth, and evidence about the pattern of change in healthy infants is sparse. This is in part because of the difficulty of gaining consent for invasive blood testing in healthy newborn infants, and ethical concerns about the potential risk of harm.

Previous reports have shown that the glucose concentration decreases immediately after birth, reaching a nadir between 30 and 90 minutes.[1-3] After the nadir, regardless of feeding, the glucose concentration increases and stabilizes by 12-48 hours, reaching concentrations consistent with adult glucose concentrations by the fourth postnatal day.

However, these studies have been performed in hospitalized infants and have used differing study designs, glucose screening regimes, and analyzers, along with differing care patterns, which were determined by hospital protocols. Comparison between studies is difficult as some are cross-sectional, others longitudinal and all report differing feeding regimes.[1-4] Importantly, all infants were in the hospital and had intermittent blood or plasma glucose measurements, sampled at varying intervals. Thus, changes in glucose concentrations between sampling were not captured.

Postnatal care has also altered considerably since these studies were undertaken. Current best practice is to establish skin-to-skin contact and breastfeeding as soon as possible after birth.[5] Infants are encouraged to feed frequently and only remain hospitalized if healthcare treatment is required.

Therefore, we sought to determine glucose concentrations in healthy, term, appropriately grown infants cared for according to current recommendations, measuring glucose concentrations using both intermittent capillary heel prick sampling (glucose oxidase method) and also continuous interstitial monitoring from soon after birth to the completion of 5 postnatal days. We sought to describe the normal postnatal changes in glucose concentrations in the current era, and to compare the incidence of low glucose concentrations in healthy infants against international recommendations for treatment of infants at risk of neonatal hypoglycemia.

CGM	Continuous glucose monitor
GLOW	Glucose in Well Babies Study

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Supported by the Waikato Sick Babies Trust and the Waikato Medical Research Foundation (grant numbers 243 and 268). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.02.079

Methods

We undertook this prospective observational cohort study at a tertiary referral hospital, birthing centers and family homes in Hamilton, New Zealand between November 2015 and August 2017. Inclusion criteria were English-speaking parents, maternal first trimester body mass index 18.5-30 kg/m^2, no pregnancy complications (including no history of maternal diabetes, drug dependency, or medications that may affect the infant's glucose concentrations), singleton birth at term (37-42 weeks), birth weight 10th-90th percentile, and Apgar score of ≥7 at 5 minutes.[6-8] Exclusion criteria were skin conditions preventing attachment of the continuous glucose monitor or if the infant was unwell for any reason.

The Glucose in Well Babies (GLOW) study was approved by the Northern A Health and Disability Ethics Committee Ref: 15/NTA/104. The study protocol is available online at http://hdl.handle.net/2292/32066.

Families were informed about the study via antenatal classes, Facebook, posters, and information sheets placed in antenatal clinics, as well as word of mouth. Interested families contacted a member of the research team, who screened for eligibility and provided further information. Written informed consent was obtained before the birth and confirmed after birth.

Families could choose to birth at the hospital, birthing center, or home. Those who chose to birth at the hospital could transfer to the primary birthing center and were discharged home within 2-3 days. The research team visited the family twice daily to take heel prick samples and record adverse events (defined as redness or swelling at the continuous glucose monitor site or unwell infant requiring medical attention).

An iPro2 continuous glucose monitor (CGM ipro2, Medtronic, MiniMed, Northridge, California) was placed in the infant's lateral thigh as soon as possible after birth using an ENLiTE inserter device (Medtronic, Minimed). Capillary heel-prick sampling commenced 60-90 minutes after this, before feeds wherever possible. Three further samples were taken 3-4 hours apart within the first 24 hours, and then 12-hourly for the next 4 days (total of ≤16 samples). All samples after discharge were collected by capillary heel-prick from warmed heels using a gentleheel lancing device (Alleset Healthcare Solutions, Amsterdam, the Netherlands).

Glucose concentrations were measured by epoc blood analyzer (Siemens Healthineers, Erlangen, Germany; reading range, 20-700 mg/dL [1.1-38.5 mmol/L][9]; coefficient of variation, 1.8%-4.1% at low plasma glucose concentrations) or blood gas analyzer if the infant was still in hospital (Radiometer ABL800 FLEX, Copenhagen, Denmark; reading range, 0.0-1080 mg/dL [0.0-60 mmol/L]; coefficient of variation, 2.1%). Both use glucose oxidase methods in whole blood and provide plasma-equivalent concentrations. Therefore, we have reported our findings as plasma glucose concentrations.

Researchers and families were blinded to all results and remained so until data collection was complete and the statistical analysis plan finalized. Glucose results were not displayed on the epoc analyzer screen. Measurements using the hospital blood gas analyzer were performed by a clinician who was not part of the study team. The IPro2 CGM does not display glucose concentration in real time.

Infants were fed according to maternal choice. At study completion, each parent was asked to confidentially complete a questionnaire which included whether they and the researchers remained blinded to the glucose concentrations.[10]

Continuous glucose data were downloaded using CGM Solutions software (version 3.0 C) and placeholder plasma glucose concentrations. After completion of recruitment, the electronic signals from the sensor were plotted against postnatal age for each infant and inspected for completeness by 2 investigators. Data that were >3 SD from the mean for the cohort were identified for possible exclusion after recalibration. Prolonged data gaps (>15 minutes) were set as missing data. The interstitial signal data were then recalibrated using actual plasma glucose concentrations and a previously reported algorithm.[11] The recalibrated data signals were again visually inspected using these criteria and excluded as necessary. Data were also excluded if they occurred before the first or after the last plasma glucose measurement, or if the interval between measurements was >13 hours.

We defined an episode of low plasma glucose concentration as any measurement <47 mg/dL (<2.6 mmol/L): severe episodes were <36 mg/dL (<2.0 mmol/L); and extremely low were <27 mg/dL (<1.5 mmol/L).[12] An episode of high plasma glucose concentration was ≥1 consecutive measurements of >144 mg/dL (>8 mmol/L), and extremely high was >180 mg/dL (>10 mmol/L).[13] Episodes of low and high interstitial glucose concentrations were defined as ≥2 consecutive glucose concentrations (10 minutes) below or above each threshold. The duration of a low interstitial glucose episode was the time from the start of the episode until the first of ≥2 consecutive measurements >47 mg/dL (>2.6 mmol/L).[14]

We determined that a sample size of 50 infants would enable an estimation of a mean glucose concentration with a 95% CI of ±3 mg/dL (0.19 mmol/L).[15] In our previous study of infants born at risk of hypoglycemia, a mean plasma glucose concentration of 258 term infants was 59 ± SD 13 mg/dL (3.3 ± 0.7 mmol/L) at 12 hours. We expected that 25% of families would withdraw after enrollment, and planned that recruitment would be complete when 50 infants had a minimum dataset, defined as ≥12 plasma glucose measurements (4 in the first 24 hours, and the final measurement at or after 118 hours); and continuous interstitial glucose measurements commencing before 4 hours and continuing to ≥120 hours. Data were uploaded to the Liggins Institute Data Hub, University of Auckland, and reviewed by the Data Manager, and the Chair of the Steering Committee, who were not involved with the clinical aspects of the study, to determine when recruitment was complete.

Plasma glucose concentrations were analyzed in 6 epochs: 0-12 hours, 12-24 hours, and each of the following four 24-hour periods. Samples collected within 1 hour of the beginning or end of an epoch could be reallocated to the adjacent epoch to achieve 2 samples in each 24-hour epoch wherever possible. Interstitial glucose concentrations were included in the analysis from 2 hours after birth.

All available data were included in the main analysis. Prespecified sensitivity analyses were performed on the subsets of infants with complete data, infants with complete plasma glucose data, and infants who received only breast milk. Complete plasma glucose data was defined as ≥12 capillary glucose concentrations, including 4 in the first 24 hours, and 2 on each of the following 4 days, and acceptable continuous glucose trace for a minimum of 8 hours in the first 12 hours, 10 hours between 12 and 24 hours of age, and 20 hours in each of the following 24-hour periods. Data were also compared between prespecified subgroups: weight loss from birth to 5 days (above vs below the median, and above vs below 10% of birthweight); maternal body mass index (18.5-24.9 vs 25.0-29.9 kg/m^2); maternal pregnancy weight gain (<11.5 vs ≥ 11.5 kg); mode of delivery (vaginal vs cesarean); sex; and gestational age (<40 vs ≥ 40 weeks).[6]

To compare plasma and interstitial glucose profiles of infants at risk of hypoglycemia (small [<10th percentile or <2.5 kg] or large [>90th percentile or >4.5 kg] or infants of mothers with diabetes) we used data from the first 48 hours after birth in the subgroup of infants born at term who participated in the Sugar Babies Study.[14] For analysis of interstitial glucose concentrations, infants were included if they had continuous signal from 4 to 48 hours.

Categorical variables are presented as number (%), with comparisons presented as risk ratios and 95% CIs. Continuous variables are presented as mean ± SD or median (minimum-maximum) and compared using mean difference and 95% CI. Mixed model analyses were used to account for repeated measures within the same infant, with covariance and residual structures chosen to minimize the Akaike information criterion, presented as mean (SE) and mean difference (95% CI). Percentile curves were calculated using the skewness median coefficient of variation (least mean squares) method[16], and fitted using LMSchartmaker Light Version 2.54 (Institute of Child Health, London, United Kingdom, 2011). Interstitial glucose concentrations were compared between gestation groups using hourly means for each infant. Glucose variability was derived as the SD of the interstitial glucose concentration within each epoch.[17] Analyses were undertaken using Stata V14.2, 2015 (Statacorp, College Station, Texas).

Results

Of 70 infants recruited, 3 were withdrawn because of illness (neonatal jaundice, seizures, and Fragile X syndrome) (**Figure 1**; available at www.jpeds.com). All other infants completed the study. Most were born vaginally, were exclusively breastfed, and the mean weight loss at 5 days was 3.0 ± 4.1% of birth weight (**Table I**; available at www.jpeds.com). All parents reported that they remained blinded to plasma glucose concentrations and that the researchers were also unaware of these. No infant showed clinical signs commonly attributed to neonatal hypoglycemia and there were no adverse events from the CGM.

The first plasma glucose concentration was obtained at mean ± SD of 2.1 ± 0.5 hours (range, 1.2-4.0 hours). The mean plasma glucose concentration over the first 120 hours was 68 ± 16 mg/dL (range, 38-119 mg/dL; 3.8 ± 0.9 mmol/L [range, 1.6-6.6 mmol/L]). Plasma glucose concentrations were essentially stable for 48 hours at 59 ± 11 mg/dL (range, 30-99 mg/dL; 3.3 ± 0.6 mmol/L [range, 1.7-5.5 mmol/L]) then increased between 48 and 72 hours, and stabilized thereafter at 83 ± 13 mg/dL (range, 43-119 mg/dL; 4.6 ± 0.7 mmol/L [range, 2.4 to 6.6 mmol/L]) (**Table II**).

Continuous glucose monitors were placed at a mean ± SD of 0.8 ± 0.4 hours of age (range, 0.2-2.0 hours), the first interstitial glucose concentrations were obtained at 2.2 ± 1.4 hours (range, 1.1-11.7 hours), and monitors remained in place for 124 ± 3 hours (range, 120-133 hours). Most infants (63 [94%]) had some data. Forty-one infants (61%) had continuous data from 4 to 120 hours of age. The mean of all interstitial glucose concentrations over the first 120 hours was 68 mg/dL (95% CI, 67-70 mg/dL [range, 27-153 mg/dL]); 3.8 (95% CI, 3.7-3.9 mmol/L [range, 1.5-8.5 mmol/L]). The interstitial glucose concentrations showed a gradual increase over the first day, from 55 ± 10 mg/dL (3.1 ± 0.6 mmol/L) between 0 and 12 hours to 59 ± 9 mg/dL (3.3 ± 0.5 mmol/L) between 12 and 24 hours and thereafter a similar pattern to plasma glucose concentrations, increasing after 48 hours from a mean of 59 ± 11 mg/dL (3.3 ± 0.6 mmol/L) to 83 ± 14 mg/dL (4.6 ± 0.8 mmol/L) after 72 hours (**Table II**). The mean glucose variability increased from 6 mg/dL (range, 5-6 mg/dL; 0.31 mmol/L [range, 0.27-0.35 mmol/L]) in the first 12 hours to 11 mg/dL (range, 4-23 mg/dL; 0.62 mol/L [range, 0.20-1.30 mmol/L]) at >96 hours.

Plasma and interstitial glucose concentration percentile curves were similar (**Figure 2**). The interstitial glucose percentiles curve shows an increase at approximately 18 hours, then remained constant until 48 hours, before increasing to a new plateau by day 4 (84-96 hours of age). The 10th percentile approximated 47 mg/dL (2.6 mmol/L) for the first 48 hours and was ≥54 mg/dL (≥3 mmol/L) after 84 hours. The 90th percentile was ≥72 mg/dL (≥4 mmol/L) in the first 48 hours and ≥90 mg/dL (≥5 mmol/L) after 72 hours. However, the glucose patterns of individual infants were variable and did not consistently follow the percentile lines, so that initial low or high glucose concentrations did not predict subsequent glucose concentrations (**Figure 3**; available at www.jpeds.com).

One-third of infants had episodes of plasma glucose concentrations <47 mg/dL (<2.6 mmol/L), most commonly in the first 12 hours (**Table III**). Some infants continued to

Table II. Plasma and interstitial glucose concentrations in postnatal age epochs, and changes after birth

Plasma glucose concentrations						Interstitial glucose concentrations					
Postnatal age (h)	Infants (n)	Measurements (n)	Glucose concentration (mg/dL [mmol/L])	Change in glucose concentration (mg/dL [mmol/L])	*P* value	Infants (n)	Measurements (n)	Duration of monitoring (h)	Glucose concentration (mg/dL [mmol/L])	Change in glucose concentration (mg/dL [mmol/L])	*P* value
0-120	67	797	68 (16) [3.8 (0.9)]			63	80 076	105.9 (28.0)	70 (17) [3.9 (0.9)]		
0-4	64	65	57 (13) [3.2 (0.7)]			60	1388	1.9 (0.6)	54 (12) [3.0 (0.6)]		
>4-12	62	94	57 (10) [3.2 (0.5)]			63	5667	7.5 (1.7)	55 (10) [3.1 (0.5)]		
0-12	67	159	57 (11) [3.2 (0.6)]	ref		63	7064	9.3 (1.9)	55 (10) [3.1 (0.6)]	ref	
>12-24	67	105	59 (10) [3.3 (0.5)]	0 (−2 to 2) [−0.0 (−0.1 to 0.1)]	.94	61	8438	11.5 (2.1)	59 (9) [3.3 (0.5)]	4 (3 to 5) [0.2 (0.2 to 0.3)]	<.001
>24-48	67	138	60 (12) [3.3 (0.7)]	2 (0 to 4) [0.1 (0.0 to 0.2)]	.03	60	16 743	23.3 (3.3)	59 (11) [3.3 (0.6)]	4 (3 to 5) [0.2 (0.2 to 0.3)]	<.001
>48-72	67	133	69 (17) [3.8 (0.9)]	11 (8 to 14) [0.6 (0.4 to 0.8)]	<.001	58	16 472	23.7 (1.8)	69 (15) [3.8 (0.8)]	14 (12 to 15) [0.8 (0.7 to 0.9)]	<.001
>72-96	67	132	82 (12) [4.6 (0.7)]	24 (21 to 27) [1.3 (1.2 to 1.5)]	<.001	58	15 996	23.0 (3.6)	82 (12) [4.5 (0.7)]	26 (24 to 29) [1.5 (1.3 to 1.6)]	<.001
>96-120	67	130	83 (11) [4.6 (0.6)]	25 (22 to 28) [1.4 (1.2 to 1.5)]	<.001	58	15 363	22.1 (4.9)	83 (14) [4.6 (0.8)]	27 (24 to 30) [1.5 (1.3 to 1.7)]	<.001

Data are number, mean (SD), for glucose concentration and duration, and mean change (95% CIs) for change with epoch 1 (0-12 hours) as reference.

have episodes of low plasma glucose concentrations up to 72 hours, and 22% (15/67) had ≥1 episode. There were no episodes of plasma glucose concentrations of <27 mg/dL (<1.5 mmol/L) or >144 mg/dL (8.0 mmol/L).

Continuous glucose monitoring showed more frequent and more severe episodes of low glucose concentration than intermittent sampling. Of the 41 infants with complete interstitial glucose data, 30 (73%) had ≥1 episode <47 mg/dL (<2.6 mmol/L), and 21 of these (70%) occurred in the first 12 hours. There was a median of 3 episodes (range, 1-8 episodes) per infant, each lasting 1.0 hour (range, 0.2-49.5 hours), with a total duration of 5.5 hours (range, 0.8-51.3 hours) per infant. Four infants continued to have episodes after 72 hours, and 1 had a first episode after 72 hours.

One-quarter of infants had ≥1 episode of interstitial glucose concentrations of <36 mg/dL (2.0 mmol/L), most of whom (80%) had episodes in the first 12 hours (**Table III**). There was a median of 1 episode (range, 1-5 episodes) per infant each lasting 1.0 hour (range, 0.3-12.1), with a total duration of 1.6 hours (range, 0.3-20.3 hours) per infant. Two infants had a first episode of <36 mg/dL (<2.0 mmol/L) after 24 hours of age. Only 4 infants (8%) had episodes of interstitial glucose concentrations of >144 mg/dL (8.0 mmol/L), and these only occurred after 96 hours (**Table III**).

The proportion of infants who experienced plasma glucose concentrations below various recommended thresholds for treatment in infants at risk of hypoglycemia ranged between 0% and 25% in the first 4 hours, and between 3% and 40% at 4-24 hours, reaching up to 46% after 48 hours (**Table IV**). These proportions were all considerably higher when interstitial glucose concentrations were considered.

Infants in this study had fewer glucose measurements than those in our previous cohort of infants born at risk of hypoglycemia (median, 6 [range, 4-7] vs median, 8 [range, 1-22]; $P < .001$). However, the incidence of low glucose concentrations was similar in the 2 groups (**Table V**; available at www.jpeds.com).

Sensitivity analyses, restricting data to infants who met the complete dataset criteria, infants who had a complete plasma metabolite dataset, or infants who received only breast milk, did not change any of the results.

In subgroup analyses, infants born at <40 weeks of gestation had approximately 5.4 mg/dL (95% CI, 1.8 to 9.0; 0.3 mmol/L [95% CI, 0.1-0.5]) lower mean plasma glucose concentrations and were more likely to have episodes of low plasma glucose concentrations (<47 mg/dL [<2.6 mmol/L]) than those born later (19/32 [59%] vs 7/35 [20%]; risk ratio, 3.0; 95% CI, 1.4-6.1; $P = .001$), but the difference in the proportion of infants with low interstitial glucose concentrations did not reach statistical significance (**Table VI**; available at www.jpeds.com). Infants born by cesarean delivery (n = 10) had lower plasma glucose concentrations than those born vaginally (n = 57) (mean, 65 mg/dL [95% CI, 59-70 mg/dL] vs 70 mg/dL [95% CI, 68-72 mg/dL]; 3.6 mmol/L [95% CI, 3.3-3.9 mmol/L] vs

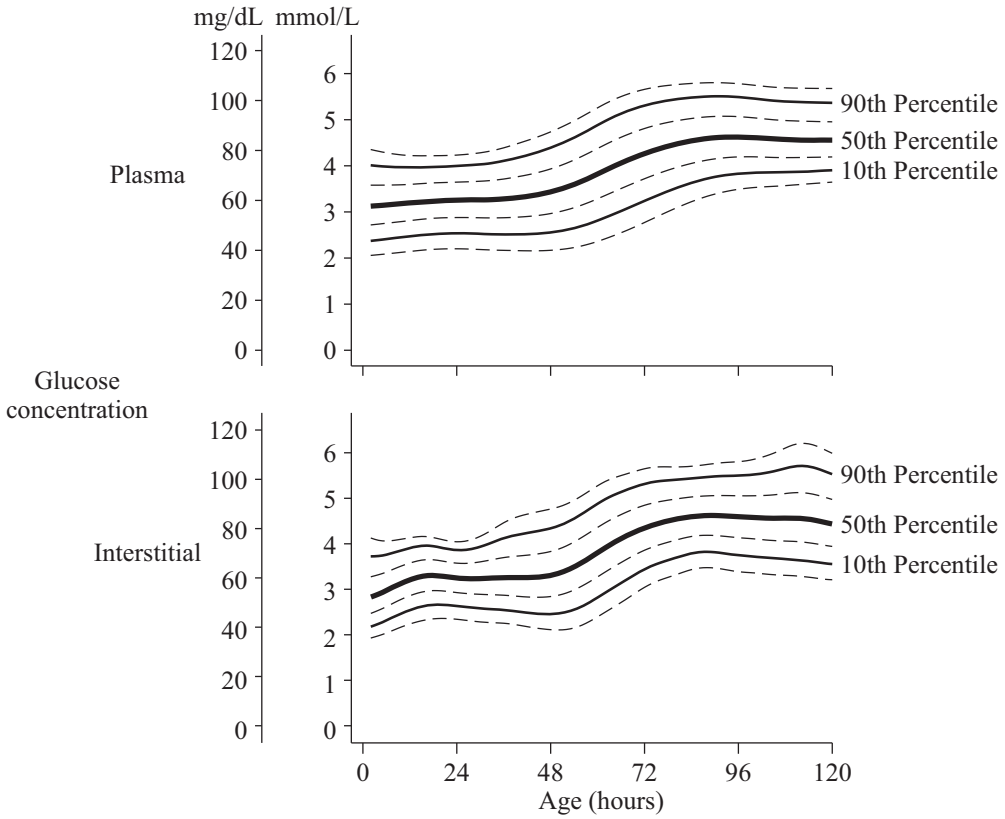

Figure 2. Glucose percentiles.

3.9 mmol/L [95% CI, 3.8-4.0 mmol/L]; $P = .03$), although the proportion with episodes of low plasma glucose concentrations was similar (4/10 [40%] vs 22/57 [39%]; risk ratio, 1.04; 95% CI, 0.45-2.37; $P = 1.00$). Infants with weight loss greater than the median (3.8%) had lower mean plasma glucose concentrations than those with less weight loss (67 mg/dL; 95% CI, 65-68 mg/dL vs 72 md/dL; 95% CI, 70-74 mg/dL, 3.7 mmol/L; 95% CI, 3.6-3.8 mmol/L vs 4.0 mmol/L; 95% CI, 3.9-4.1 mmol/L; $P = .002$). Only 3 infants had a weight loss of >10% of birthweight. There were no differences in plasma glucose concentrations related to maternal body mass index, maternal weight gain during pregnancy, or sex of the infant (data not shown).

Discussion

We describe plasma and interstitial glucose concentration profiles over the first 5 postnatal days from a cohort of

Table III. Numbers of infants who experienced low and high plasma and interstitial glucose concentrations over the first 120 hours after birth

Postnatal ages (h)	Plasma glucose concentrations (mg/dL [mmol/L])					Interstitial glucose concentrations (mg/dL [mmol/L])				
	Infants (n)*	<27 [< 1.5]	<36 [< 2.0]	<47 [< 2.6]	>144 [>8.0]	Infants (n)*	<27h [< 1.5]	<36 [< 2.0]	<47 [< 2.6]	>144 [> 8.0]
0-120	67	0	7 (10)	26 (39)	0	41	0	10 (24)	30 (73)	4 (10)
0-4	64	0	3 (5)	12 (19)	0	60	0	4 (7)	24 (40)	0
>4-12	62	0	1 (2)	11 (18)	0	63	1 (2)	9 (14)	31 (49)	0
0-12	67	0	4 (6)	18 (27)	0	57	1 (2)	9 (16)	33 (58)	0
>12-24	67	0	2 (3)	8 (12)	0	58	0	3 (5)	20 (34)	0
>24-48	67	0	2 (3)	9 (13)	0	57	0	5 (9)	20 (35)	0
>48-72	67	0	2 (3)	7 (10)	0	56	0	1 (2)	17 (30)	0
>72-96	67	0	0 (0)	1 (1)	0	53	0	0	1 (2)	0
>96-120	67	0	0 (0)	0 (0)	0	49	0	0	4 (8)	4 (8)

Data are number (%).
*For plasma glucose, n is the number of infants with any data in that epoch. For interstitial glucose, n is the number of infants with acceptable data for a minimum of 8 hours in the first 12 hours, 10 hours between 12 and 24 hours of age, 20 hours in each of the following 24-hour periods, and all of these for 0-120 hours.

Table IV. Numbers of infants with episodes of glucose concentrations below recommended thresholds for treatment

Postnatal ages (h)	0-4	4-24	24-48	48-72	72-120
American Academy of Pediatrics*					
Plasma	0/64 (0)	2/67 (3)	1/67 (1)	1/67 (1)	0/67 (0)
Interstitial	0/60 (0)	6/55 (11)	3/57 (5)	1/56 (2)	0/47 (0)
British Association of Perinatal Medicine†					
Plasma	3/64 (5)	3/67 (4)	2/67 (3)	2/67 (3)	0/67 (0)
Interstitial	4/60 (7)	9/55 (16)	5/57 (9)	1/56 (2)	0/47 (0)
World Health Organisation‡					
Plasma	12/64 (18)	16/67 (24)	9/67 (13)	7/67 (10)	1/67 (1)
Interstitial	23/60 (38)	35/55 (63)	19/57 (33)	17/56 (30)	4/47 (9)
Pediatric Endocrine Society§					
Plasma	16/64 (25)	27/67 (40)	15/67 (22)	31/67 (46)	4/67 (6)
Interstitial	30/60 (50)	40/55 (73)	33/57 (58)	41/56 (73)	26/47 (55)

Data are number (%).
*<25 mg/dL [1.4 mmol/L] if 4 hours, <35 mg/dL [1.9 mmol/L] if 4-24 hours.[18]
†<36 mg/dL [2.0 mmol/L].[19]
‡< 47 mg/dL (2.6 mmol/L).[20]
§50 mg/dL (2.8 mmol/L) in the first 48 hours, ≤60 mg/dL (3.3 mmol/L)] after 48 hours.[21]
The American Academy of Pediatrics and Pediatric Endocrine Society guidelines refer to plasma glucose concentrations. The British Association of Perinatal Medicine and World Health Organisation guidelines refer to whole blood glucose concentrations.

term, healthy, appropriately grown infants who were cared for by their parents in their own homes, and the majority of whom were exclusively breastfed. Our data show that overall there are 2 distinct increases in glucose concentrations, the first over the first 18 hours and the second after 48 hours, reaching a new plateau by 96 hours at concentrations similar to adult concentrations.[22] This glucose profile suggests that healthy infants have completed their metabolic transition by day 4.

An immediate decrease in plasma glucose concentrations soon after birth has been previously described in hospitalized term infants.[1-3] Presumably, these changes result from cutting the umbilical cord and interruption of the continuous supply of glucose from the mother. We did not see this early decrease in plasma glucose concentrations, although we observed a small increase in interstitial glucose concentrations over the first 18 hours, suggesting an earlier decrease may have occurred. Despite placing the continuous glucose sensors as soon after birth as possible, sensors require an hour for wetting before the signal is reliable, and data are not available until after the initial calibrating plasma glucose measurement taken after this time.[23] For this reason, the interstitial glucose percentiles begin 2 hours after birth, and we may have missed an initial decrease in glucose concentrations before this. However, as current best practice for term infants is to establish breastfeeding and skin-to-skin care as soon as possible, it is also possible that these practices contribute to a smaller postnatal fall in glucose concentrations than has been previously reported.[24,25] Nonetheless, if a plasma glucose concentration is taken after 2 hours in healthy term infants, one can expect a mean plasma glucose concentration of 59 mg/dL (3.3 mmol/L), and a concentration <47 mg/dL (<2.6 mmol/L) is below the 10th percentile. These findings are similar to 2 small earlier reports which measured whole blood glucose at 48 hours (pooled samples n = 41) with an overall mean ± SD concentration of 61 ± 13 mg/dL (3.4 ± 0.7 mmol/L).[2,26]

We found that the mean plasma glucose concentration remains lower than adult concentrations for the first 48 hours and reasonably stable, increasing to a mean of 83 mg/dL (4.6 mmol/L) only after 72 hours, similar to earlier reports.[2,3] The exact mechanisms of postnatal metabolic adaptation are complex. The primary function of fetal insulin is the regulation of fetal growth, and insulin secretion is regulated at a lower glucose concentration in the fetus than it is after birth.[27] Healthy newborn infants have higher plasma insulin concentrations than older children, despite lower glucose concentrations.[28,29] It is possible that suppression of insulin secretion and establishment of regulation at a higher glucose concentration is gradual process, and the time required for this contributes to the lower plasma glucose concentrations in the first 48 hours after birth.[30] After 72 hours, the mean plasma glucose concentrations continued to gradually increase to reach normal adult ranges, suggesting that this metabolic transition is completed by this time. A plasma glucose concentration of < 54 mg/dL (3.0 mmol/L) after 84 hours was <10th percentile in our cohort.

A report of 200 healthy breastfed term appropriately grown infants hospitalized in India (mean birthweight, 2650 g; range, 2300-4290 g) with 800 plasma glucose measurements between 3 and 72 hours after birth did not show an increase in glucose concentrations between 24 and 72 hours.[31,32] Infants from the earlier study were hospitalized, breastfed every 1.5-2.0 hours after the first 6 hours, and each infant had fewer plasma glucose measurements than infants in our cohort. These factors may have decreased the opportunity to detect changes in glucose concentrations with increasing postnatal age.

Although the mean glucose concentrations in our cohort showed these 2 distinct phases of increase, we also found that glucose concentrations varied widely in individual infants. Importantly, unlike growth percentiles, which can be useful to predict subsequent growth trajectory and detect perturbations, our glucose percentiles are not useful for predicting glucose trajectories of individual infants. An infant with an initial plasma glucose concentration on the 3rd percentile did not predictably remain close to the 3rd percentile for the first 5 days. Rather, individual infants appeared to take varying periods of time to stabilize their glucose concentrations, suggesting immature regulatory mechanisms during this transitional phase.

We found that term infants born at <40 weeks of gestation had lower plasma glucose concentrations than those born after 40 weeks and were also more likely to have episodes of low glucose concentrations. Similar to late preterm infants, who are identified as being at risk for hypoglycemia, our data

suggest that healthy early term infants are more likely to have low plasma glucose concentrations than more mature infants. Others have reported that early term infants are at higher risk of poorer outcomes than term infants born later.[33]

There are few issues related to the care of newborn infants that have caused as much controversy as neonatal hypoglycemia.[34,35] In an attempt to standardize care and decrease the burden of harm caused by hypoglycemia, recommendations for screening infants at risk and thresholds for treatment have been developed.[18-21] However, there is considerable variation in these recommendations, reflecting the limited evidence upon which they are based. Our data show that many healthy infants have glucose concentrations below the international recommended thresholds for treatment in at-risk infants. Other investigators have reported incidences of low glucose concentrations in healthy term infants between 14% and 29% within the first 48 hours depending on the definition of low glucose applied, with 10% continuing to have episodes up to 72 hours.[4,32,36] Our findings show that episodes of low glucose concentrations are more common that previously reported. Applying the definition of <47 mg/dL (<2.6 mmol/L), 39% of infants in our cohort had episodes of low plasma glucose and 73% had episodes of low interstitial glucose concentrations during the first 48 hours.

We found that the frequency of low plasma glucose concentrations in the first 48 hours was similar in this cohort of term healthy infants and in an earlier cohort of at-risk infants, although concentrations <27 mg/dL (1.5 mmol/L) were uncommon in healthy infants. Previously we have reported that, among children born at risk of hypoglycemia, those who became hypoglycemic were more likely to experience decreased executive and visual motor functioning aged 4.5 years than those who did not become hypoglycemic.[37] We are unable to determine if similarly low glucose concentrations in healthy infants also may be associated with impairments in later childhood.[38]

A key strength of the GLOW study was the study population of healthy infants whose care was similar to that of many contemporary newborns in developed countries. Glucose concentrations were measured using reliable glucose oxidase analysis and continuous interstitial glucose monitoring. Potential weaknesses of our study are a relatively small sample size and limited data within the first 2 hours after birth. In addition, the iPro2 interstitial glucose analyzer has not been specifically validated at low glucose concentrations, although we used offline point-to-point calibration so that inaccuracies of the inbuilt algorithms at these concentrations would not have affected our findings. It was also not always possible to take heel prick samples before feeds, which may have added some variability to the measurements, but is unlikely to have significantly influenced the overall pattern of glucose changes within the cohort as a whole.

We conclude that, in term healthy infants, mean glucose concentrations increased over the first 18 hours, and then were stable to 48 hours, before increasing to adult concentrations after 72 hours, suggesting that metabolic transition was complete by the fourth day. However, the pattern of glucose concentrations varied widely in individual infants, so that early glucose measurements did not predict later low or high plasma glucose concentrations. Many infants had episodes of low glucose concentrations below widely accepted intervention thresholds for at-risk infants. ■

We thank all the participating infants and families, without whom this study would not have been possible; the GLOW nurses Alana Cumberpatch, Kelly Ashton, Leanne Baker, Ellen Berney, and Rebecca Sisterson for their commitment to the study; Stephen Du Toit, Laboratory Manager, Waikato Hospital, Hamilton for assistance with data management; and Safayet Hossin, Maternal and Perinatal Central Coordinating Research Hub, Liggins Institute, University of Auckland, for assistance with data management.

Submitted for publication Nov 20, 2019; last revision received Feb 16, 2020; accepted Feb 27, 2020.

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Data Statement

Data sharing statement available at www.jpeds.com.

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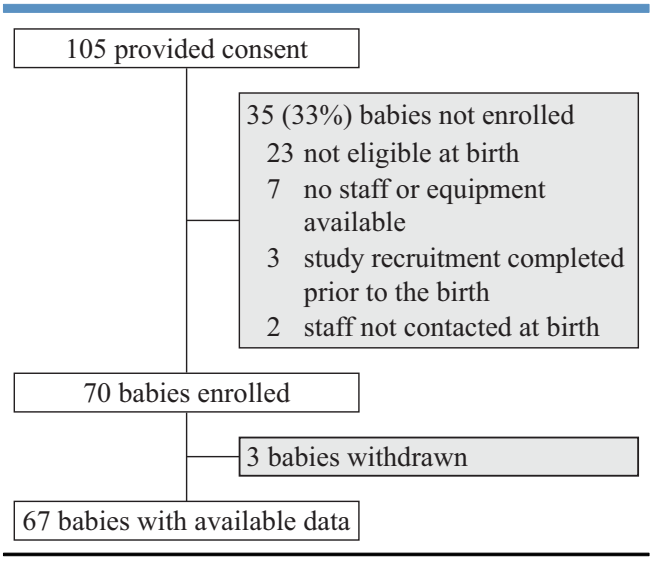

Figure 1. Trial profile.

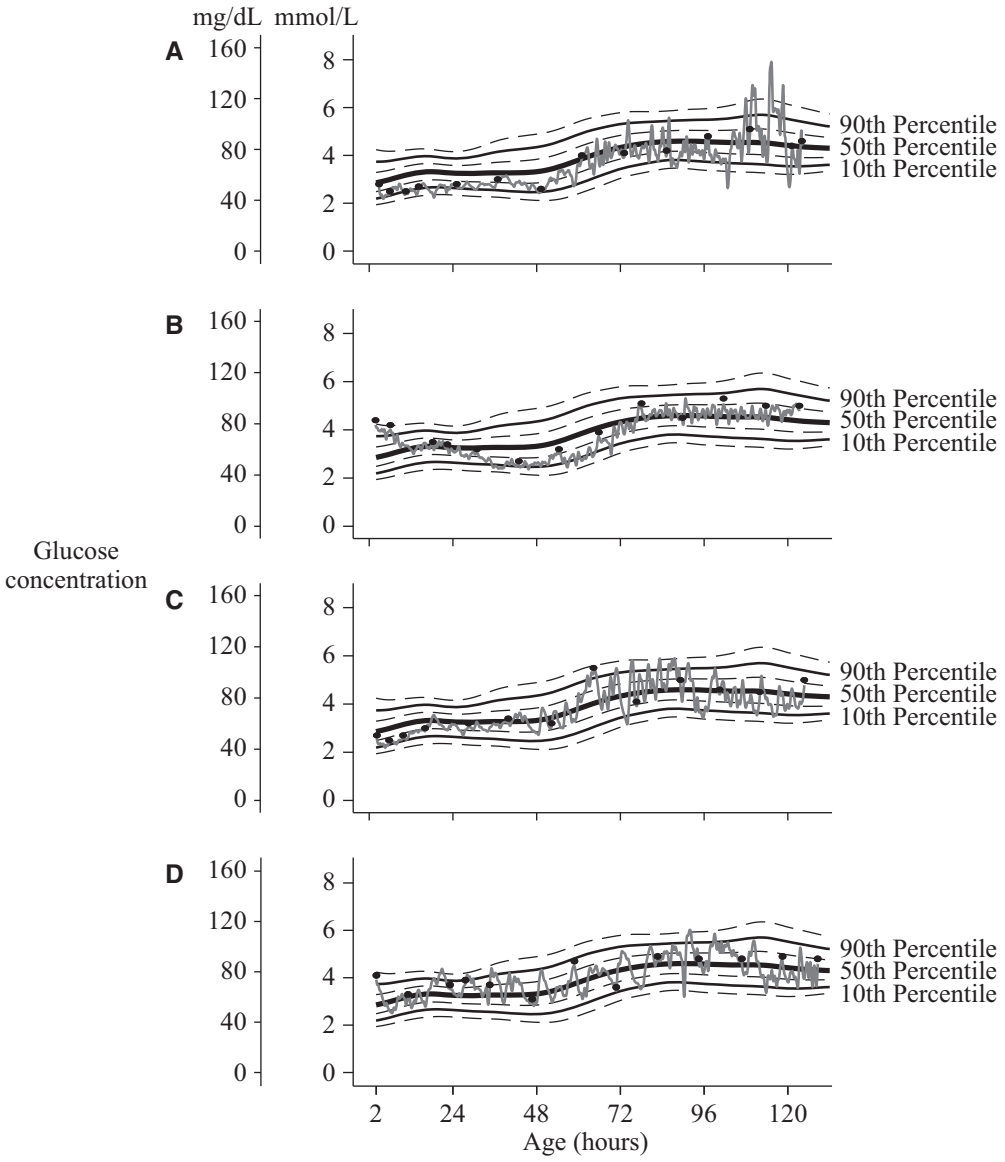

Figure 3. Four individual infants. Circles are plasma glucose measurements, grey lines are continuous interstitial glucose concentrations.

Table I. Characteristics of mothers and infants

Characteristics	Mean (SD) or number (%)
Mother (n = 67)	
Age (y)	32.3 (4.1)
Parity	0 (0-3)
BMI at booking (kg/m^2)	23.5 (2.6)
Weight gain during pregnancy (kg)	13.2 (4.6)
Vaginal birth	57 (85)
Cesarean delivery	10 (15)
Arrival home after birth (h)	60.9 (19.5)
Infant (n = 67)	
Gestation (wk)	40.1 (1.2)
Male sex	41 (61)
Ethnicity	
New Zealand European	56 (84)
Maori	2 (3)
Other	9 (13)
Birth weight (g)	3584 (349)
Weight (z score)	0.36 (0.7)
Length (cm)	51.5 (1.8)
Length (z score)	0.60 (0.81)
Head circumference (cm)	35.3 (1.2)
Head circumference (z score)	0.73 (0.94)
Weight change from birth (g)	−112 (149)
Weight loss from birth (% of birthweight)	3.0 (4.1)
Exclusively breastfed	57 (85)
Received expressed human milk	23 (34)
Received infant formula	10 (15)

BMI, body mass index.
Data are mean (SD) or number (%).

Table V. Number of healthy and at-risk infants with episodes of low glucose concentrations

Thresholds, mg/dL [mmol/L]	Plasma glucose				Interstitial glucose			
	Healthy infants	At-risk infants	Risk ratio (95 % CI)	*P* value	Healthy infants	At-risk infants	Risk ratio (95 % CI)	*P* value
<47 [2.6]	26/67 (39)	159/326 (49)	0.80 (0.58-1.10)	.14	37/51 (68)	33/44 (75)	0.97 (0.76-1.23)	.82
<36 [2.0]	7/67 (10)	48/326 (15)	0.71 (0.34-1.50)	.44	12/51 (23)	14/44 (32)	0.74 (0.38-1.43)	.49
<27 [1.5]	0/67 (0)	9/326 (3)	0	.37	0/51 (2)	3/44 (3)	0	.10

Data are number (%).
Healthy infants are from the current (GLOW) study. At-risk infants were term infants from the Sugar Babies Study[14] (refer to Methods).

Table VI. Comparison of glucose concentrations in the first 120 hours after birth between infants who were born at <40 or ≥40 weeks of gestation

	Plasma glucose (mmol/L)				Interstitial glucose (mmol/L)*			
Postnatal ages (h)	<40 wk	≥40 wk	Mean difference (95% CI)	*P* value	<40 wk	≥40 wk	Mean difference (95% CI)	*P* value
0-120	3.6 (0.9)	3.9 (0.9)	0.29 (0.11 to 0.46)	<.01	3.8 (0.9)	4.0 (0.9)	0.28 (0.07 to 0.49)	<.01
0-4	2.9 (0.7)	3.4 (0.7)	0.52 (0.18 to 0.87)	<.01	2.8 (0.6)	3.3 (0.7)	0.58 (0.28 to 0.89)	<.01
>4-12	3.0 (0.5)	3.3 (0.5)	0.28 (0.05 to 0.52)	.02	3.0 (0.5)	3.2 (0.5)	0.25 (0.03 to 0.47)	.03
0-12	3.0 (0.6)	3.4 (0.6)	0.38 (0.14 to 0.63)	<.01	2.9 (0.6)	3.2 (0.6)	0.33 (0.11 to 0.55)	<.01
>12-24	3.1 (0.6)	3.4 (0.5)	0.27 (0.04 to 0.50)	.02	3.2 (0.5)	3.4 (0.5)	0.27 (0.05 to 0.50)	.02
>24-48	3.2 (0.6)	3.5 (0.7)	0.26 (−0.01 to 0.53)	.06	3.2 (0.5)	3.4 (0.6)	0.30 (0.03 to 0.56)	.03
>48-72	3.7 (1.0)	3.9 (0.9)	0.13 (−0.23 to 0.48)	.49	3.7 (0.8)	3.9 (0.8)	0.17 (−0.17 to 0.51)	.33
>72-96	4.4 (0.6)	4.7 (0.7)	0.30 (0.03 to 0.56)	.03	4.4 (0.6)	4.7 (0.6)	0.22 (−0.00 to 0.44)	.05
>96-120	4.4 (0.5)	4.8 (0.6)	0.34 (0.13 to 0.56)	<.01	4.5 (0.6)	4.7 (0.8)	0.19 (−0.04 to 0.43)	.11

Glucose concentration data are mean (SD) or mean (95% CI).
*Interstitial data are reduced to hourly means to enable modelling to work regarding comparison of means.