

Gender and glycaemia: Insulin sensitivity and secretion in premature neonates

Jennifer Dickson*, J. Geoffrey Chase*, Cameron Gunn*, Christopher Pretty*,
Adrienne Lynn**, Jane Alswailer**

* Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand
(e-mail: jennifer.dickson@pg.canterbury.ac.nz, geoff.chase@canterbury.ac.nz)

** Neonatal Department, Christchurch Women's Hospital, Christchurch, New Zealand

*** Department of Paediatrics: Child and Youth Health, Auckland, New Zealand
& Liggins Institute, University of Auckland, Auckland, New Zealand

Abstract: The inability to regulate blood glucose concentration (BG) is a common complication of prematurity and stress in neonatal intensive care, particularly in very low birth weight (VLBW) neonates. Model-based glycaemic control requires quantification of glucose and insulin appearance, clearance, and action. In the VLBW neonates plasma insulin concentration is often used to reflect insulin secretion due to sampling limitations. In this study, C-peptide concentrations are used to more accurately analyse insulin secretion in a VLBW neonatal cohort, and a comparison of insulin secretion and sensitivity is made between male and female sub cohorts. The retrospective analysis is made of a cohort comprises 88 extremely pre-term (median age 26 [25–27] weeks) and very low birth-weight infants (median birth weight 793 [691-901 g]). In 41 of the infants, C-Peptide plasma concentrations were used in conjunction with C-peptide models to estimate insulin secretion. Time varying model-based insulin sensitivity values are also fit across dense clinical data from the entire 88 patients. Female infants had higher insulin secretion than males ($P < 0.005$) for comparable BG and plasma insulin concentrations. Females also had a higher correlation of increasing insulin secretion with increasing BG ($R^2 = 0.51$) than males ($R^2 = 0.13$), and were more insulin sensitive ($P < 0.005$), and had greater hour to hour variability in this sensitivity ($P < 0.005$). The results suggest female neonates are better able to clear insulin, and probably reflect the worsened outcomes and increased complications in male neonates, reported in the literature.

1. INTRODUCTION

Glycaemic variability, resulting in hyper- or hypoglycaemia, is a common complication of prematurity and stress in neonatal intensive care units (NICUs) (Beardsall et al., 2010). Elevated blood glucose (BG) (hyperglycaemia) in extremely preterm babies has been associated with greater mortality and morbidity (Hall et al., 2004, Hays et al., 2006). Low BG (hypoglycaemia) is associated with adverse neurodevelopmental outcomes (Lucas et al., 1988).

There is currently no best practice method or target for glycaemic control in preterm babies and BG is often controlled by varying nutritional input (Alswailer et al., 2007), which may restrict infant growth (Thabet et al., 2003) and cause adverse neurodevelopmental outcomes (Ehrenkranz et al., 2006). Insulin allows greater amounts of parenteral dextrose to be administered, and increases weight gain (Vaucher et al., 1982, Ostertag et al., 1986, Collins et al., 1991), but often results in excessive protocol induced hypoglycaemia (Beardsall et al., 2007, Alswailer et al., 2012), which may adversely affect neurodevelopmental outcomes (Lucas et al., 1988). Metabolic variability is a leading cause of this problem (Chase et al., 2011). Fixed or *ad hoc* protocols are often utilised, which lack patient specificity or rely extensively on clinical judgement (Tsubahara et al., 2012), thus having minimal ability to manage variability.

STAR (Stochastic TARgeted) glycaemic control is a model-based decision support tool. STAR uses a physiological model-based estimate of insulin sensitivity (SI) to describe a patient's current metabolic state, and potential future variability. Insulin dosage is recommended such that predictions in BG outcomes overlap with a clinically desired target range. In the NICU, it has shown promising results, with 74% time in target band (4.0-8.0 mmol/L) and 3-5 times less hypoglycaemia than other published studies (Le Compte et al., 2012). Tightness and safety in control can be improved further through increased accuracy of the glucose-insulin system, narrowing SI prediction bounds to reflect peripheral insulin sensitivity changes more accurately.

A critical aspect when modelling the glucose-insulin regulation system is the endogenous secretion of insulin by the pancreas. In extremely low birth weight (ELBW) preterm infants, clinical sampling limitations mean insulin secretion cannot be quantified directly. All prior studies into neonatal insulin secretion have relied on plasma insulin levels alone as an indicator of increased insulin secretion. However, insulin is highly unreliable in this role given its multiple clearance pathways, as well as the variability between these pathways (Le Compte, 2009). C-peptide concentration is a much better predictor of insulin secretion due to its much simpler and less variable clearance kinetics (Van Cauter et al., 1992).

This paper looks at the effect gender has on insulin sensitivity and secretion, with the aim of quantifying sources of variability in SI, and improving glycaemic forecasting and control in this cohort.

2. METHODS

2.1 Patient Cohort

Data used were collected from 88 preterm neonates during a prospective, randomised glycaemic control trial (Alsweiler et al., 2012). Infants were eligible if they were born at <30 weeks gestational age, or birth weight <1500g, and had become hyperglycaemic (two BGC measures >8.5 mmol/L more than 4 hours apart). Exclusion criteria included hyperglycaemia secondary to an iatrogenic dose of glucose, major congenital malformation, or judged to be dying. Infants were randomised when the infant was hyperglycaemic (4-5 days postnatal age).

All nutritional input, blood glucose concentrations, and insulin infusions were recorded along with weight and size. SI profiles were fit using data from infants who received insulin. Data was considered adequate for fitting SI where BG measurements were taken at least every 6 hours, patients were receiving insulin with a lapse of no more than 6 hours, and were 12 hours or more in length. From some study patients had more than one episode fitted. SI was fit according to clinically validated methods (Le Compte et al., 2010), and compared between male and female infants.

Blood samples were taken from each infant at randomisation (day of randomisation (DOR) = 0), 7 and 14 days after randomisation (DOR = 7 and 14 respectively) and 36 weeks. Plasma insulin and glucose concentrations were determined, and remaining plasma samples were frozen. BG concentrations were taken as clinically indicated using a glucose oxidise method (ABL 700, Radiometer Ltd, Copenhagen, Denmark). Plasma insulin concentrations were measured on an Azsym system auto-analyzer (Abbott Laboratories, Abbott Park, IL) (Alsweiler et al., 2012). Retrospective C-peptide analysis was carried out on some of the frozen samples if there was sufficient remaining blood from samples taken 0-15 days after randomisation, and GA<32 weeks. C-peptide concentrations were determined using immunometric assays (Elecsys 2010, Roche Diagnostics, Germany). Cohort characteristics across the blood samples are given in Table 1.

2.2 C-peptide Model Equations and calculation of Endogenous Insulin Secretion

C-peptide is secreted in equimolar quantities with insulin, but is only cleared by the kidney. In comparison, insulin is cleared by liver and periphery in a highly variable manner, as well as through the kidneys. Therefore, the relatively simple kinetics of C-peptide provide a better means to estimate insulin secretion using a 2 compartment kinetics model (Van Cauter et al., 1992):

$$\frac{dC}{dt} = S - (k_1 + k_3)C + k_2Y \quad (1)$$

$$\frac{dY}{dt} = k_1C - k_2Y \quad (2)$$

Where C is the concentration of C-peptide in the central compartment of plasma (and tissues in rapid equilibrium with

the plasma), and Y is the concentration of C-peptide in the peripheral extra vascular compartment. S is the rate at which C-peptide (and insulin) is secreted into the central compartment. The rate parameters k_1 and k_2 describe the rate of transport of C-peptide from the central to the peripheral compartment, and vice versa. The parameter k_3 describes the irreversible renal clearance of C-peptide from the central compartment via the kidney (Van Cauter et al., 1992).

Sampling constraints due to limited blood volume in this cohort mean frequent, serial measurements of C-peptide were not possible. Given the available data and the fact that nutrition was delivered by constant infusion that did not vary much hour-to-hour, a steady-state assumption can be made to enable deconvolution of the insulin secretion rate from measured C-peptide. Under this steady-state assumption, it follows from Equation 2 that the rate of C-peptide entering and leaving the peripheral compartment must be equal. Substituting this equality into Equation 1 yields:

$$S = k_3C \quad (3)$$

Since insulin is secreted in equimolar quantities with C-peptide, under steady state conditions the steady state rate insulin secretion is directly proportional C-peptide in the central compartment.

Since no studies have been performed in preterm or term neonates to determine C-peptide kinetics, adult data and methodology (Van Cauter et al., 1992) were used as an approximation. Neonatal patients are assumed normal (not obese or diabetic), so a short half-life of 4.95 min and a fraction, F , of 0.96 was used. The long half-life thus was calculated (Van Cauter et al., 1992):

$$\text{long-half life (min)} = 0.14 \text{ Age (years)} + 29.2. \quad (4)$$

Hence, the estimated long half-life is 29.2 minutes for newborns.

Table 1: Patient characteristics. Numbers are presented as median [interquartile range] where appropriate. TGC is tight glycaemic control. DOR is the day after randomisation, with day of enrolment being DOR=0.

	Whole cohort	Blood samples
Number of Patients		
Total	88	41
Control group	45	21
TGC group	43	20
Male n (%)	42 (48%)	20(49%)
Number of samples	-	54
Birth weight, g	793 [691-901]	839 [735-1000]
Gestational age, wks	26 [25-27]	27 [26- 29]
Post natal age, days		
At Enrolment	4 [3-7]	3.5 [3-6.5]
At time of Sample	N/A	9.5 [4 -17]
DOR, days	N/A	7 [0 - 14]
Ethnicity		
Asian	10	9 (22%)
Caucasian	12	11 (27%)
Maori	15	17 (41%)
Pacific Island	6	4 (10%)

The kinetic parameters were then calculated using these cohort specific values, as per (Van Cauter et al., 1992):

$$k_2 = F(b - a) + a \quad (5)$$

$$k_3 = \frac{a b}{k_2} \quad (6)$$

Where $a = \log(2)/(\text{short half-life})$, and $b = \log(2)/(\text{long half-life})$. The resulting calculated value for k_3 for all neonates was $k_3=0.0644 \text{ min}^{-1}$, which is within the reported normal clearance rates in adults (Eaton et al., 1980, Polonsky et al., 1986, Van Cauter et al., 1992).

2.3 NICING model of glucose-insulin dynamics

The NICING (Neonatal Intensive Care Insulin-Nutrition-Glucose) model describes glucose-insulin dynamics in the extremely preterm neonate. The rate of change of blood glucose (G), in [mmol/L/min], is defined:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P_{ex}(t) + EGP m_{body} - CNS m_{brain}}{V_{g,frac}(t) m_{body}} \quad (7)$$

Insulin-mediated glucose clearance is determined by S_I , and non-insulin-mediated uptake includes a clearance term p_G and a central nervous system (CNS) uptake. Glucose sources include exogenous glucose, $P_{ex}(t)$, and endogenous production, EGP . m_{body} is the body mass, and m_{brain} the brain mass (~14% of m_{body}). S_I is a patient-specific, time-varying, estimate of insulin sensitivity that captures a patient's current metabolic state. The lower limit of S_I is enforced at $1e-7$, which is near zero, to ensure that physiological correctness.

The rate of change of plasma (I) and interstitial (Q) insulin (units [mU/L/min]) are defined:

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L) u_{en} \quad (8)$$

$$\dot{Q} = n_I (I(t) - Q(t)) - n_C \frac{Q(t)}{1 + \alpha_Q Q(t)} \quad (9)$$

Plasma insulin is cleared via the liver, n_L , the kidney, n_K , and transport into interstitial fluid, n_I . Insulin enters the system exogenously, u_{ex} , or endogenously, u_{en} , through pancreatic secretion. Insulin leaves interstitial fluid via degradation, n_C .

SI profiles for each patient were fit using integral based fitting methods (Hann et al., 2005) and Equations 7-9, on a retrospective hour-to-hour basis. SI is assumed constant over an hour, and a linear interpolation between BG values was used as an initial estimate of the glucose model. Insulin sensitivity variability was evaluated as the difference between SI values 1 and 4 hours apart.

2.4 Statistical Analysis

Non-parametric data are presented as median with interquartile range (IQR). Non parametric data group comparisons were analysed by the Mann-Whitney U-test, and the Kruskal-Wallis test, which extends the Mann-Whitney U-test to more than 2 samples. Cumulative distributions were used to compare the incidence of SI and SI variability across their range. The two-sample Kolmogorov-Smirnov test used to compare the shape of cumulative distributions. Correlations were calculated using a linear least squares regression analysis. Differences between samples were considered statistically significant if $p \leq 0.05$

Table 3: Comparison of results by sub cohorts. Data are presented as median [IQR]

	All Samples			No Exogenous Insulin only		
	Male	Female	P	Male	Female	P
n	25	29	-	15	25	-
n (DOR=0)	11	13		8	11	
Weight [g]	930 [755-1041]	815 [702-975]	0.15	930 [730-1044]	845[725-991]	0.49
GA [wks]	26 [25 - 27]	26 [25 - 26.3]	0.60	26 [25 - 27]	26 [25.3 - 27]	0.51
PNA	9 [3.8-16.5]	11 [4.8-17]	0.71	6 [3-17]	11 [4.8-17]	0.38
BG [mmol/L]	6.9 [5.5-10.2]	7.6 [4.9-10.8]	0.77	8.0 [5.6-11.6]	7.6 [4.9-10.8]	0.79
Plasma Insulin [mU/L]	14 [6.8 - 26]	16 [8.9 - 7]	0.52	10.4 [3.5 - 30.8]	14.3 [8.9 - 27.1]	0.34
C-peptide [nmol/L]	0.510 [0.166 - 0.860]	1.083 [0.464 - 1.603]	P< 0.005	0.655 [0.212 - 1.144]	1.278 [0.786-1.603]	0.03
Insulin Secretion [mU/L/kg/min]	4.7 [2.1-8.3]	11.7 [5.3 - 18.7]	0.003	5.6 [2.5-11.1]	13.8 [7.7 - 18.7]	0.03
Average Total Dextrose Intake [mg/kg/min]	9.4 [7.7-11.1]	9.3 [7.8 - 11.8]	0.79	9.2 [6.6-10.1]	9.4 [8.1-11.9]	0.36
PN glucose [g/day]	5.0 [0-8.8]	3.6 [0-8.4]	0.29	7.9 [3.7-9.9]	3.6 [0-9.0]	0.11
EN lactose [g/day]	2.6 [0.7-11.9]	6.5 [0.5-19.6]	0.74	1.5 [0.5-8.2]	6.5 [0.5-15.2]	0.24
Protein Intake that day [g/kg]	3.1 [2.5-3.9]	2.8 [2.6-3.8]	0.39	2.9 [2.3-3.8]	2.9 [2.7-3.8]	0.92
Number receiving insulin	10	4		-	-	-
Insulin at sample [U/kg/hr]	0.00 [0.00-0.05]	0.00 [0.00-0.00]	0.06	-	-	-
Total Insulin that day [U/kg]	0.00 [0.18-0.64]	0.00 [0.00-0.48]	0.10	0.00 [0.00-0.27]	0.00 [0.00-0.09]	0.40

3.0 RESULTS

Across all samples, median BG was 7.5 mmol/L [inter-quartile range 5.1 – 10.5 mmol/L], median Plasma Insulin 14.3 mU/L [inter-quartile range 8.5 - 26.2 mU/L], and median C-peptide concentration was 2.3 nmol/L [inter-quartile range 1.1 - 4.2 nmol/L].

Females had higher endogenous insulin secretion than males ($P < 0.003$) (Table 3). There was no effect from sex on weight at the time of the sample, BG, plasma insulin concentration or gestational age ($P \geq 0.15$). Ethnicity did not affect the endogenous insulin secretion ($P = 0.29$). Exclusion of samples where in the infant was receiving an exogenous insulin infusion (14 of 54 samples) still resulted in a significant difference between male and female neonates ($P = 0.03$) with regards to insulin secretion, but nothing else ($P \geq 0.11$). Insulin secretion remained significantly different between the sexes at $DOR = 0$ and $DOR > 0$ ($P = 0.01$, $P = 0.05$, respectively).

From the HINT data, a total of 160 patient episodes from 55 patients were fit, totalling 4680 hours and 1391 BG measurements. Across these episodes, the median GA was 25 weeks (IQR 24-26 weeks), and average weight was 720g (IQR 688-906g). Median BG measurement interval was 4 hours (IQR 3.5-4.8), and median insulin infusion rate was 0.05 U/kg/hr (IQR 0.03-0.07 U/kg/hr). Insulin sensitivity and its variability in female neonates was higher than males ($P < 0.05$), as was insulin sensitivity variability ($P < 0.05$), shown in Figure 1.

SI profiles were generated using the BG based secretion models shown in Figure 2. There was a weak relationship between insulin secretion and BG (Figure 2), Female neonates had the strongest correlation of insulin secretion with BG (Figure 2), with a weak correlation for males. The difference between the sexes in insulin secretion was true over the entire BG range. Thus, Figure 2 also shows separate male and female models for secretion in these cohorts, as well as an overall cohort method.

4.0 DISCUSSION

The results show a clear difference in C-peptide concentrations between male and female infants, and model-based analysis suggests it means that endogenous insulin secretion is higher in the female sub-cohort. Insulin secretion in female infants was more than double that in the males, despite similar demographics and insulin and blood glucose concentrations. With the observed similarities in BG between the sexes, increased insulin secretion for similar plasma insulin concentrations would imply increased clearance of insulin.

There was a positive relationship between BG concentration and insulin secretion rate (Figure 2). Higher insulin secretion at higher BG concentrations has been reported previously in preterm babies (Hawdon et al., 1995) and is supported by research that shows that a drop in plasma glucose in hyperglycaemic preterm infants is accompanied by a decrease in insulin secretion (Mitanchez-Mokhtari et al., 2004). This correlation was much stronger in females, suggesting that the

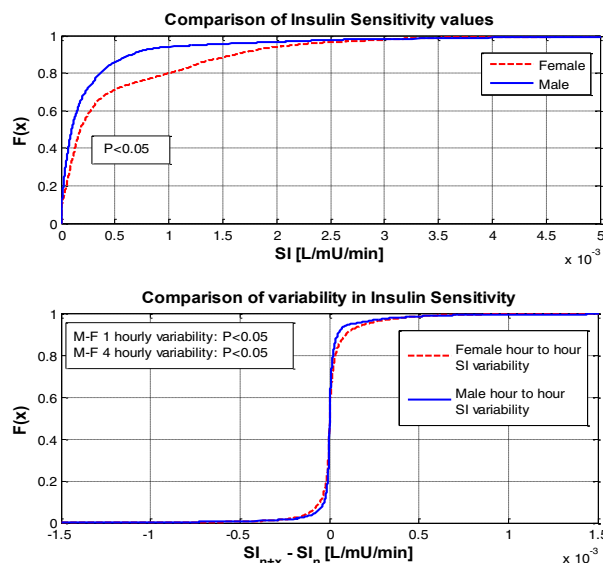


Figure 1: Comparison of insulin sensitivity (SI) and SI variation for male and female subcohorts. Subscript n denotes a current SI, and n+x to denote a future SI x hours later. F(x) is cumulative fraction of sample values across a variables range.

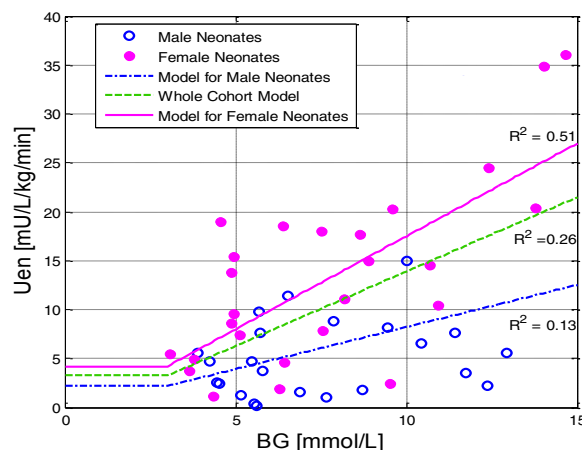


Figure 2: Models of endogenous insulin secretion as a function of BG over the whole cohort, and male and female sub cohorts. 5 data points from 54 total (9%) were excluded from the analysis as outliers based on a 2-3 fold difference with other data points of similar BG. Most of these data points were from heavier and older patients of $GA > 29$ weeks. However, 2 were from 26 week old male and female neonates

male sub cohort was sicker and less able to consistently respond to their metabolic environment.

Across all sufficiently dense clinical data from the HINT cohort, model based SI was higher in females than males. This model based insulin sensitivity is a ‘whole body’ sensitivity, and includes both peripheral insulin sensitivity and deviations from modelled glucose and insulin dynamics.

Thus, in this case, higher insulin sensitivity in female premature neonates implies greater peripheral sensitivity to insulin or lower endogenous glucose production, or both. Increased variability in hour to hour insulin sensitivity at a

higher insulin sensitivity potentially implies increased ability to respond to their metabolic environment, but makes insulin-based control more difficult.

Greater and more metabolically consistent insulin secretion, as well as higher insulin sensitivity, also suggests higher maturation of the glucose-insulin system and greater clinical stability. This result matches clinical expectations.

It is well established in literature that more premature infants are male than female, with roughly 55% of preterm neonates being male (Hoffman and Bennett, 1990, Cooperstock and Campbell, 1996, Elsmén et al., 2004). In addition, outcomes are worse in male premature neonates, with higher mortality (Hoffman and Bennett, 1990, Elsmén et al., 2004, Peacock et al., 2012) and morbidity. Premature male neonates of GA<29 weeks tend to be more likely to require mechanical ventilation, have higher chronic lung disease, and need more inotrope support (Elsman et al., 2004). Higher incidence of respiratory distress syndrome (RDS) has been used to imply lower lung maturation in male neonates. Male gender has been associated with greater hospital length of stay, pulmonary haemorrhage, postnatal steroids, and major cranial abnormalities (Peacock et al., 2012). In short, the greater inherent fragility of the male neonate is well documented.

For model based glycaemic control purposes, gender can be used to quantify some of the glycaemic variability seen over the entire cohort, and justify the use of sex-based insulin secretion models and insulin sensitivity forecasting models.

This study presents a subset of results from a larger analysis looking to estimate insulin secretion in VLBW preterm neonates using a C-peptide kinetics model in conjunction with blood glucose and plasma insulin concentrations. Insulin secretion was not found to be strongly predicted by weight, GA, ethnicity, BG, or daily glucose or protein intake [not yet published].

4.2 Study Limitations

The major assumption of this research is that of steady state kinetics. This assumption is reasonable in premature infants where the majority of nutrition is given enterally or via parenteral infusions that do not tend to change dramatically from hour to hour. Given the limited blood volume of infants, particularly extremely preterm infants, it is not possible to take multiple C-peptide measurements over a short period of time. Thus, further information about the kinetics of plasma insulin and C-peptide are not possible at this time.

Further, adult kinetic parameters, adjusted for age, were used because of the inability to comprehensively derive parameters for the neonatal cohort. If the resulting insulin secretion is also calculated using k_3 kinetic values that are approximately 2 standard deviations ($k_3 = [0.05, 0.07]$) from the normal kinetics reported and the neonatal cohort falls within the observed adult range in healthy and unhealthy cohorts, then the insulin secretion could be in error by up to ~20%. However, changing the population constant kinetic parameters does not change any of the results or trends observed, and only shift these trends.

In addition, it is not possible in this cohort to determine patient specific values for C-peptide kinetics. For the purposes of model based control, the k_3 parameter used is thus sufficient. Finally, any scale inaccuracies are absorbed and scale the time varying patient-specific insulin sensitivity parameter (Le Compte et al., 2010) without significantly altering control outputs.

6.0 CONCLUSIONS

C-peptide has been used to give a better estimate of insulin secretion in a very low birth weight cohort, where previous studies have relied on plasma insulin levels alone. Female neonates had a stronger endogenous insulin secretion relationship with BG than males, and that, overall, BG was the best predictor for endogenous insulin secretion. For glycaemic control, these results suggest that differing insulin secretion models can be used between the sexes. Insulin sensitivity and variability was also higher in females, suggesting an increased ability of this sub-cohort to respond glycaemically. The results reflect documented worsened outcomes and increased complications seen for premature male neonates.

7.0 REFERENCES

- Alsweiler, J. M., Harding, J. E. & Bloomfield, F. H. 2012. *Tight glycaemic control with insulin in hyperglycaemic preterm babies: a randomized controlled trial.* Pediatrics, 129, 639-47.
- Alsweiler, J. M., Kuschel, C. A. & Bloomfield, F. H. 2007. *Survey of the management of neonatal hyperglycaemia in Australasia.* Journal of Paediatrics and Child Health, 43, 632-635.
- Beardsall, K., Vanhaesebrouck, S., Ogilvy-Stuart, A., Ahluwalia, J., Vanhole, C., Palmer, C., Midgley, P., Thompson, M., Cornette, L., Weissenbruch, M., Thio, M., De Zegher, F. & Dunger, D. 2007. *A randomised controlled trial of early insulin therapy in very low birth weight infants, "NIRTURE" (neonatal insulin replacement therapy in Europe).* BMC Pediatrics, 7, 29.
- Beardsall, K., Vanhaesebrouck, S., Ogilvy-Stuart, A. L., Vanhole, C., Palmer, C. R., Ong, K., Vanweissenbruch, M., Midgley, P., Thompson, M., Thio, M., Cornette, L., Ossuetta, I., Iglesias, I., Theyskens, C., De Jong, M., Gill, B., Ahluwalia, J. S., De Zegher, F. & Dunger, D. B. 2010. *Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study.* J Pediatr, 157, 715-9 e1-3.
- Chase, J. G., Le Compte, A. J., Suhaimi, F., Shaw, G. M., Lynn, A., Lin, J., Pretty, C. G., Razak, N., Parente, J. D., Hann, C. E., Preiser, J.-C. & Desai, T. 2011. *Tight glycaemic control in critical care - The leading role of insulin sensitivity and patient variability: A review and model-based analysis.* Computer Methods and Programs in Biomedicine, 102, 156-171.

- Collins, J., Hoppe, Brown, K., Edidin, D., Padbury, J. & Ogata, E. 1991. *A controlled trial of insulin infusion and parenteral nutrition in extremely low birth weight infants with glucose intolerance.* Journal of Pediatrics, 118, 921 - 927.
- Cooperstock, M. & Campbell, J. 1996. *Excess males in preterm birth: interactions with gestational age, race, and multiple birth.* Obstet Gynecol, 88, 189-93.
- Eaton, R. P., Allen, R. C., Schade, D. S., Erickson, K. M. & Standefer, J. 1980. *Prehepatic insulin production in man: kinetic analysis using peripheral connecting peptide behavior.* J Clin Endocrinol Metab, 51, 520-8.
- Ehrenkranz, R. A., Dusick, A. M., Vohr, B. R., Wright, L. L., Wrage, L. A. & Poole, W. K. 2006. *Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants.* Pediatrics, 117, 1253-61.
- Elsmen, E., Hansen Pupp, I. & Hellstrom-Westas, L. 2004. *Preterm male infants need more initial respiratory and circulatory support than female infants.* Acta Paediatr, 93, 529-33.
- Elsmén, E., Steen, M. & Hellström-Westas, L. 2004. *Sex and gender differences in newborn infants: why are boys at increased risk?* The Journal of Men's Health & Gender, 1, 303-311.
- Hall, N., Peters, M., Eaton, S. & Pierro, A. 2004. *Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis.* Journal of Pediatric Surgery, 39, 898 - 901; discussion 898-901.
- Hann, C. E., Chase, J. G., Lin, J., Lotz, T., Doran, C. V. & Shaw, G. M. 2005. *Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model.* Comput Methods Programs Biomed, 77, 259-270.
- Hawdon, J. M., Hubbard, M., Hales, C. N. & Clark, P. M. 1995. *Use of specific immunoradiometric assay to determine preterm neonatal insulin-glucose relations.* Arch Dis Child Fetal Neonatal Ed, 73, F166-9.
- Hays, S., Smith, E. & Sunehag, A. 2006. *Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants.* Pediatrics, 118, 1811 - 1818.
- Hoffman, E. L. & Bennett, F. C. 1990. *Birth-Weight Less Than 800 Grams - Changing Outcomes and Influences of Gender and Gestation Number.* Pediatrics, 86, 27-34.
- Le Compte, A. 2009. *Modelling the Glucose-Insulin Regulatory System for Glycaemic Control in Neonatal Intensive Care.* PhD thesis, University of Canterbury.
- Le Compte, A., Chase, J. G., Russell, G., Lynn, A., Hann, C., Shaw, G., Wong, X. W., Blakemore, A. & Lin, J. 2010. *Modeling the glucose regulatory system in extreme preterm infants.* Comput Methods Programs Biomed.
- Le Compte, A. J., Lynn, A. M., Lin, J., Pretty, C. G., Shaw, G. M. & Chase, J. G. 2012. *Pilot study of a model-based approach to blood glucose control in very-low-birthweight neonates.* BMC Pediatr, 12, 117.
- Lucas, A., Morley, R. & Cole, T. J. 1988. *Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia.* Br Med J, 297, 1304-1308.
- Mitanchez-Mokhtari, D., Lahlou, N., Kieffer, F., Magny, J.-F., Roger, M. & Voyer, M. 2004. *Both Relative Insulin Resistance and Defective Islet β -Cell Processing of Proinsulin Are Responsible for Transient Hyperglycemia in Extremely Preterm Infants.* Pediatrics, 113, 537-541.
- Ostertag, S., Jovanovic, L., Lewis, B. & Auld, P. 1986. *Insulin pump therapy in the very low birth weight infant.* Pediatrics, 78, 625-630.
- Peacock, J. L., Marston, L., Marlow, N., Calvert, S. A. & Greenough, A. 2012. *Neonatal and infant outcome in boys and girls born very prematurely.* Pediatr Res, 71, 305-10.
- Polonsky, K. S., Licinio-Paixao, J., Given, B. D., Pugh, W., Rue, P., Galloway, J., Karrison, T. & Frank, B. 1986. *Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients.* J Clin Invest, 77, 98-105.
- Thabet, F., Bourgeois, J., Guy, B. & Putet, G. 2003. *Continuous insulin infusion in hyperglycaemic very-low-birth-weight infants receiving parenteral nutrition.* Clin Nutr, 22, 545-7.
- Tsubahara, M., Shoji, H., Mori, M., Matsunaga, N., Ikeno, M., Hisata, K., Okumura, A. & Shimizu, T. 2012. *Glucose metabolism soon after birth in very premature infants with small- and appropriate-for-gestational-age birth weights.* Early Hum Dev, 88, 735-8.
- Van Cauter, E., Mestrez, F., Sturis, J. & Polonsky, K. S. 1992. *Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance.* Diabetes, 41, 368-77.
- Vaucher, Y. E., Walson, P. D. & Morrow, G., 3rd 1982. *Continuous insulin infusion in hyperglycemic, very low birth weight infants.* Journal of pediatric gastroenterology and nutrition, 1, 211-7.