



Peripartum Management of Glycemia in Women With Type 1 Diabetes

Naomi Achong,¹ Emma L. Duncan,¹
H. David McIntyre,² and Leonie Callaway¹

OBJECTIVE

We aimed to 1) describe the peripartum management of type 1 diabetes at an Australian teaching hospital and 2) discuss factors influencing the apparent transient insulin independence postpartum.

RESEARCH DESIGN AND METHODS

We conducted a retrospective review of women with type 1 diabetes delivering singleton pregnancies from 2005 to 2010. Information was collected regarding demographics, medical history, peripartum management and outcome, and breast-feeding. To detect a difference in time to first postpartum blood glucose level (BGL) >8 mmol/L between women with an early (<4 h) and late (>12 h) requirement for insulin postpartum, with a power of 80% and a type 1 error of 0.05, at least 24 patients were required.

RESULTS

An intravenous insulin infusion was commenced in almost 95% of women. Univariate analysis showed that increased BMI at term, lower creatinine at term, longer duration from last dose of long- or intermediate-acting insulin, and discontinuation of an insulin infusion postpartum were associated with a shorter time to first requirement of insulin postpartum ($P = 0.005$, 0.026 , 0.026 , and <0.001 , respectively). There was a correlation between higher doses of insulin commenced postpartum and number of out-of-range BGLs ($r[36] = 0.358$, $P = 0.030$) and hypoglycemia ($r[36] = 0.434$, $P = 0.007$). Almost 60% had at least one BGL <3.5 mmol/L between delivery and discharge.

CONCLUSIONS

Changes in the pharmacodynamic profile of insulin may contribute to the transient insulin independence sometimes observed postpartum in type 1 diabetes. A dose of 50–60% of the prepregnancy insulin requirement resulted in the lowest rate of hypoglycemia and glucose excursions. These results require validation in a larger, prospective study.

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¹The University of Queensland, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia

²The University of Queensland, Mater Health Services, Mater Medical Research Institute, South Brisbane, Queensland, Australia
Corresponding author: Naomi Achong, n.achong@uq.edu.au.

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In women with type 1 diabetes, glycemic control at conception, during pregnancy, and at delivery correlates with maternal and fetal outcome. Consequently, treating practitioners aim for strict glycemic control prepregnancy and during gestation. A less stringent approach is often adopted postpartum.

Pregnancy is a state of insulin resistance, with a major contribution from placental hormones. Loss of the feto-placental unit at delivery increases insulin sensitivity. Anecdotally, women may not require insulin for hours to days after delivery. The prevalence and duration of this phenomenon is poorly documented and the underlying mechanisms are unknown. Similarly, women who do require insulin in the early postpartum period commonly require reduced insulin doses. There is also an increased risk of hypoglycemia postpartum once insulin is reintroduced. This risk is thought to be exaggerated in women who breast-feed. Further, there are many and varied approaches to the reintroduction and/or titration of insulin postpartum.

The aims of this study were 1) to describe the peripartum management of type 1 diabetes at our institution and 2) to discuss the factors associated with the duration of apparent transient insulin independence postpartum.

RESEARCH DESIGN AND METHODS

We performed a retrospective chart review of women with type 1 diabetes who delivered at our institution from 2005 to 2010. Women were identified using a pre-existing database. Inclusion criteria were 1) a clinical diagnosis of type 1 diabetes prepregnancy, 2) delivery and peripartum management occurring at our institution, and 3) first available pregnancy. Exclusion criteria were 1) a clinical diagnosis of type 2 diabetes or gestational diabetes and 2) multiple pregnancies. Women on a continuous subcutaneous insulin infusion (CSII) were included.

Data were collected using chart abstraction. Information included patient demographics, medical and diabetic history, peripartum glycemic management, pregnancy complications, fetal outcome, and breast-feeding. The

timing, route of administration, and form of insulin and the blood glucose levels (BGLs) in the peripartum period were recorded. Blood ketones are not routinely recorded in women peri- or postpartum at our institution.

Data were available for 52 singleton pregnancies in 36 women. Eleven women had two pregnancies, and two women had three pregnancies. For statistical analyses, only the first available pregnancy was considered for women who had more than one singleton pregnancy during the study period. Statistical analyses were performed with the inclusion and exclusion of women on CSII (given the small numbers treated with this modality). The results remained unchanged, and, therefore, women on a CSII have been included in the analysis presented. Comparisons between women on CSII and multiple daily injections (MDI) and between types of infant feeding (breast-feeding compared with artificial feeding) were not performed due to the small numbers of women in each group.

The study received approval from the human research and ethics committee at our institution (HREC/12/QRBW/333).

Statistics

Statistical analysis was performed with SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL). Comparisons were undertaken using two-tailed Fisher exact or χ^2 tests for categorical variables and independent Student *t* tests for continuous variables. Data are shown as absolute number and percentages for categorical variables, and mean and SD for continuous variables. Normality was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Where necessary, data were transformed using logarithmic transformation. Where applicable, ranges and median values are also presented. Univariate regression analyses were performed with time to first dose of insulin in the postpartum period as the dependent variable.

A two-tailed *P* value of <0.05 was considered statistically significant. There was no published literature regarding insulin recommencement postpartum to enable a sample size to be calculated. However, we had

previously conducted an audit that demonstrated a mean time of 5.5 h (SD 6.7) to insulin recommencement postpartum. To detect a difference in time to first BGL >8.0 mmol/L postpartum between women with an early (<4 h) and late (>12 h) requirement for insulin postpartum, with a power of 80% and a type 1 error of 0.05, at least 24 patients were required.

RESULTS

The prepregnancy characteristics of the cohort are shown in Table 1. The peripartum management of women with more than one singleton pregnancy is shown in Supplementary Table 1.

Insulin Treatment

In early pregnancy, three women were treated with a CSII, three with twice-daily premixed insulin, and the remainder with a basal/bolus regimen. The three women on premixed insulin were changed to basal/bolus regimens. The small numbers of women managed with a CSII precluded comparative analysis with women on MDI. Changes in the insulin treatment prepregnancy and at term are presented in Supplementary Table 2.

Pregnancy and Delivery Characteristics

The delivery and pregnancy outcome characteristics are shown in Table 1. There were no differences in outcomes between women with an early (<4 h) and late (>12 h) requirement for insulin postpartum. The average length of gestation of women receiving betamethasone ($n = 11$) was 35 weeks and 0 days, compared with 36 weeks and 4 days for the entire cohort. Of the 11 vaginal deliveries, 4 were spontaneous and 7 induced. Twenty-five women (69%) required a caesarean section: 3 elective and 22 emergency procedures (9 for maternal and 13 for fetal indications).

Peripartum Management

At our institution, the joint policy of the obstetric medicine, obstetric, and endocrinology departments is to recommend an intravenous neutral insulin (Actrapid)/dextrose infusion (Supplementary Data, protocol) once a woman is in established labor or has ceased oral intake prior to caesarean

Table 1—Characteristics of women

	All women (n = 36)	Early requirement for insulin* (n = 12)	Intermediate requirement for insulin* (n = 20)	Late requirement for insulin* (n = 4)	P value**
Prepregnancy characteristics					
Maternal age in years [mean (SD)]	27.3 (5.1)	28.0 (3.5)	27.1 (6.1)	25.5 (2.9)	0.220
BMI at prepregnancy [mean (SD)]	26.8 (4.5)	28.9 (5.9)		23.6 (2.8)	0.091
Duration diabetes in years [mean (SD)]	14.9 (8.0)	16.7 (7.5)	15.8 (7.8)	13.0 (9.7)	0.443
Primigravida [n (%)]	18 (50.0)	7 (58.3)	8 (40.0)	3 (75.0)	1.000
HbA _{1c} at diagnosis, % [mean (SD)]	8.2 (2.0)	7.3 (1.4)	9.0 (1.7)	7.2 (0.9)	0.142
HbA _{1c} at diagnosis, mmol/mol [mean (SD)]	64 (20.6)	56.3 (15.3)	74.9 (18.4)	55.2 (9.8)	0.142
Microvascular disease [n (%)]	8 (25.0)	2 (16.7)	5 (25.0)	1 (25.0)	1.000
Pregnancy characteristics					
Betamethasone within 72 h of delivery [n (%)]	11 (30.6)	5 (41.7)	7 (35.0)	1 (25.0)	1.000
Weight gain at term, kg [mean (SD)]	12.4 (6.4)	13.8 (6.8)	11.8 (6.6)	13.4 (4.2)	0.936
Gestation at delivery [mean (SD)]	36+3 (3)	35+5 (4)	37+1 (2)	33+4 (4)	0.309
HbA _{1c} at term, % [mean (SD)]	6.4 (1.5)	6.3 (0.8)	6.5 (2.0)	6.9 (1.2)	0.243
HbA _{1c} at term, mmol/mol [mean (SD)]	45 (11.1)	45.4 (8.3)	47.5 (20.4)	51.9 (13.1)	0.243
Change in HbA _{1c} at term, % [mean (SD)]	−1.6 (2.0)	−1.1 (1.1)	−2.1 (1.8)	−0.3 (0.5)	0.214
Change in HbA _{1c} at term, mmol/mol [mean (SD)]	−14.8 (19.8)	10.9 (12)	24.0 (17.6)	3.3 (3.3)	0.214
Delivery characteristics					
Mode of delivery					
Vaginal delivery [n (%)]	11 (30.6)	2 (16.7)	7 (35.0)	2 (50.0)	0.245
Caesarean section [n (%)]	25 (69.4)	10 (83.3)	13 (65.0)	2 (50.0)	0.245
Maternal complications					
Pregnancy-induced hypertension [n (%)]	3 (8.3)				
Pre-eclampsia [n (%)]	9 (25.0)				
HELLP syndrome [n (%)]	1 (2.8)				
Antepartum hemorrhage [n (%)]	2 (5.6)				
Cholestasis of pregnancy [n (%)]	6 (16.7)				
Acute pulmonary edema [n (%)]	1 (2.8)				
Any complication [n (%)]	22 (61.1)	6 (50.0)	14 (70.0)	2 (50.0)	1.000

*Early refers to insulin requirement in <4 h, intermediate 4–12 h, and late >12 h from delivery. **P value compares early and late insulin requirement.

section. The insulin infusion is ceased at delivery, although the dextrose is often continued until oral intake resumes. An intravenous insulin infusion was used in almost 95% of all patients and ceased at delivery in 76% (Table 2). All patients on CSII were changed to an intravenous infusion prior to delivery and the CSII was ceased. The timing of first oral intake was recorded. The dextrose infusion was ceased once oral intake was tolerated in ~60% of women. However, the timing of cessation of the dextrose infusion was not recorded in the remainder. The duration of labor was not recorded, as some women presented to the hospital in active labor. However, the timing of insulin administration (both antepartum and postpartum) was recorded.

The reintroduction of insulin in most women was based on BGL ≥ 8.0 mmol/L ($n = 24$), or, less commonly, ≥ 10 mmol/L ($n = 9$). In the remaining women, the BGL prompting the recommencement of

insulin was not stated. In the postpartum period, the first BGL reading of ≥ 8.0 mmol/L occurred an average of 9.9 h (range 1–55, SD 11.3) after delivery. The average time to first oral intake after delivery was 7.4 h (SD 4.3). There was no correlation between time to first oral intake and time to first BGL > 8.0 mmol/L ($r[35] = 0.083$, $P = 0.637$) or frequency of hypoglycemic episodes ($r[35] = -0.183$, $P = 0.293$).

From delivery until discharge, most patients had unstable glycemic control. On average, patients had two episodes of hyperglycemia daily (BGL ≥ 10 mmol/L) (mean 1.8, SD 1.2) and one hypoglycemic episode (BGL < 3.5 mmol/L) every 2nd day (mean 0.5, SD 0.6). The average duration of postpartum monitoring was 95.1 h (SD 27.7).

Apparent Transient Insulin Independence

At this institution, there was no defined policy concerning the management of

women on a CSII after delivery. In the three women on a CSII, the pump was immediately recommenced on cessation of intravenous insulin (within 48 h of delivery, zero time without insulin). The transition from intravenous insulin to CSII occurred once the patient was tolerating a normal diet. In all patients, insulin was required for glycemic control.

Twelve (33%) women on MDI required insulin within 4 h of delivery (see Supplementary Fig. 1). However the longest period without insulin was 28 h. There was variability in the timing of last dose of insulin prior to delivery (Table 2). There were no differences in the prepregnancy, pregnancy, or delivery characteristics of the women with an early compared with late requirement for insulin postpartum. The characteristics of the four patients who did not require insulin for the first 12 h postpartum are shown in Supplementary Table 3.

Table 2—Peripartum management of insulin

Insulin administration	All women (n = 36)	Early requirement for insulin* (n = 12)	Intermediate requirement for insulin* (n = 20)	Late requirement for insulin* (n = 4)	P value**
Duration of time of last dose of intermediate or long-acting insulin to delivery, h [median (IQR)]	17 (12)	26 (19)	16 (11)	17 (1.5)	0.134
Duration of time of last dose of subcutaneous short or rapid-acting insulin to delivery, h [median (IQR)]	14 (10)	14 (12)	13 (9)	14 (9.3)	0.609
Insulin infusion					
Infusion used peripartum [n (%)]	34 (94.4)	12 (100.0)	18 (90.0)	4 (100.0)	1.000
Ceased at delivery [n (%)]	26 (76.5)	7 (63.6)	19 (95.0)	0	0.089
Time to first dose of intermediate or long-acting insulin postdelivery, h [median (IQR)]	14 (19)	22 (17)	15 (13)	30 (7)	0.867
Time to first dose of rapid-acting or short-acting insulin postdelivery, h [median (IQR)]	5 (5.5)	0 (2.3)	6 (4)	22.8 (10.9)	<0.001
Time to first dose of any subcutaneous insulin after delivery, h [median (IQR)]	5 (5.3)	0 (2.3)	6 (3)	22.8 (10.9)	<0.001
Insulin required within 4 h [n (%)]	12 (33.3)	NA	NA	NA	
Insulin required in 4–12 h [n (%)]	20 (55.6)	NA	NA	NA	
Insulin required in 12–24 h [n (%)]	2 (5.6)	NA	NA	NA	
Insulin required in >24 h [n (%)]	2 (5.6)	NA	NA	NA	

*Early refers to insulin requirement in <4 h, intermediate 4–12 h, and late >12 h from delivery. **P value compares early and late insulin requirement.

Univariate regression analyses showed that a shorter time to first requirement of insulin postpartum significantly correlated with a higher BMI at term ($P = 0.005$), lower creatinine at term ($P = 0.026$), longer time from last dose of long- or intermediate-acting insulin (prior to delivery) ($P = 0.026$), discontinuation of an insulin infusion postpartum ($P < 0.001$), and greater number of BGLs >10 mmol/L postpartum ($P = 0.013$) (Table 3).

Recommendation of Regular Basal/Bolus Insulin Treatment

Insulin was first administered as short- or rapid-acting in 30 (90.9%) and intermediate- or long-acting in 2 (6.1%) women. In the remaining one woman (3.0%), both forms were commenced concurrently. In the 24 h after recommencement of insulin, 29 (80.6%) women had at least one BGL of >10 mmol/L; of these, 11 women had at least one BGL >15 mmol/L. Similarly, 17 (47.2%) women had one BGL <3.5 mmol/L; of these, 6 had at least one reading <2.0 mmol/L. Using Pearson product-moment correlation, there was a statistically significant correlation between increasing dose of insulin and number of out-of-range BGLs ($r[36] = 0.358$, $P = 0.030$) and risk of hypoglycemia ($r[36] = 0.434$, $P = 0.007$).

Table 4 shows the relationship between glucose levels and dose of insulin. Relative to the prepregnancy insulin requirement, the total daily dose of insulin recommenced was lower in 25 (69.4%), equal in 5 (13.9%), and greater in 6 (16.7%) women. There was

significant variability in the dose prescribed according to the specialty background of the prescriber (see Supplementary Fig. 2). Physicians and physician trainees prescribed insulin doses less than or equal to the prepregnancy requirement. In contrast,

Table 3—Univariate correlation analysis between time to first dose of any insulin and potential predictive variables

	Adjusted R^2	β	P
Prepregnancy characteristics			
Age	0.026	−0.036	0.829
Duration of diabetes	0.027	−0.020	0.906
Characteristics at term			
BMI at term	0.178	−0.447	0.005
HbA _{1c} at term	0.023	0.065	0.697
Creatinine at term	0.126	0.393	0.026
Hypertensive maternal disease	0.018	0.095	0.569
Delivery characteristics			
Gestation at delivery	0.024	−0.060	0.720
Mode of delivery	0.017	−0.208	0.210
Peripartum drug administration			
Vasodilators administered peripartum	0.020	−0.088	0.600
Peripartum steroids	0.005	−0.150	0.369
Peripartum glycemic management and control			
Duration of time from last dose of long- or intermediate-acting insulin until delivery	0.115	−0.376	0.026
Magnitude of last dose of long- or intermediate-acting insulin prior to delivery	0.001	−0.175	0.315
Insulin infusion postpartum	0.338	0.597	<0.001
Time to first oral intake	0.043	−0.268	0.120
Number of BGLs >10 mmol/L postpartum	0.136	−0.399	0.013
Breast-feeding	0.014	−0.114	0.494

Table 4—Percentage of prepregnancy insulin recommenced and resultant glycemic control within 24 h

	Mean insulin dose (percentage of prepregnancy dose)	Number of patients (total = 36)
Number of out-of-range BGLs		
0–1 BGL out of range*	52.4%	7
2–3 BGLs out of range*	75.3%	21
4–6 BGLs out of range*	81.5%	8
Risk of hypoglycemia		
Low (0 BGLs <3.5)	59.5%	19
Moderate (1–2 BGLs <3.5)	85.6%	16
High (3–4 BGLs <3.5)	100%	1

*Out-of-range BGLs defined as <3.5 or >10.0 mmol/L.

all women prescribed initial insulin doses greater than the prepregnancy requirement had this initiated by obstetric trainees. There was a significant correlation between the health care practitioner and dose of insulin prescribed ($r[36] = 0.728$, $P < 0.001$) and risk of hypoglycemia within 24 h of restarting insulin ($r[36] = -0.339$, $P = 0.040$) but not the risk of hyperglycemia ($r[36] = -0.001$, $P = 0.995$).

Breast-feeding

Thirty-two women (88.9%) attempted to breast-feed. In 15 women (46.9%), it was documented that advice regarding the risk of hypoglycemia was provided by a medical practitioner or lactation consultant. Given the small percentage of women who commenced artificial feeding compared with those attempting breast-feeding, comparisons of the characteristics of these women and the glycemic behavior were not performed.

CONCLUSIONS

In this retrospective study, we presented our peripartum management of women with type 1 diabetes at our institution and described their glycemic control immediately postpartum. We found that the duration of apparent transient insulin independence postpartum inversely correlated with time from the last dose of intermediate- or long-acting insulin and the continuation of an insulin infusion postpartum. More out-of-range BGLs and episodes of hypoglycemia were observed in patients recommenced on higher doses of insulin compared with those recommenced at 50–60% of the prepregnancy dose.

Prior studies concerning peripartum glycemic control have focused on neonatal outcomes. Good glycemic control during delivery minimizes neonatal hypoglycemia (1–5) and possible long-term neurological sequelae (6,7). Hence, since the first report of an insulin infusion in labor (8), this has become the mainstay of management (9,10) to achieve good glycemic control in labor (2,3,11–14). In our study, 95% of women were managed with an insulin infusion. Other approaches include subcutaneous insulin sliding scale (9,15–17), rotating fluids (9,18), or fixed dose of an intermediate insulin (19,20). Similar glycemic control has been reported with these regimens. Notably, up to 50% of women may not require insulin during induction (21), although these data were not corrected for time from last dose of insulin prior to delivery.

During active labor, insulin requirements decrease, along with an increased need for glucose (16,22,23). The latter is driven by an increase in glucose utilization and metabolic clearance (24,25). At delivery, expulsion of the feto-placental unit abruptly reduces the maternal serum concentration of hormones mediating insulin resistance. This improves maternal insulin sensitivity, decreases insulin requirements, and increases the risk of hypoglycemia (8,12,15,20,26). Consequently, a glucose infusion is often advised postpartum (4,12,17,19,20). At delivery, the insulin infusion is usually ceased (4,11,21,22) or decreased (2,8,13,27) until the patient has sufficient oral intake or significant hyperglycemia or ketosis occurs. At our institution, the insulin infusion was

ceased at delivery in ~75% of cases with continuation of dextrose only. The timing of cessation of the dextrose infusion was recorded in only 60% of cases, thereby precluding analysis of the data.

In women undergoing an elective caesarean section, 25–50% of the dose of long- or intermediate-acting insulin is recommended, usually to be administered the evening before delivery (28).

Apparent Transient Insulin Independence

Anecdotally, women can have a period of apparent transient insulin independence lasting 24–72 h (12). In our study, two women did not require insulin for at least 24 h after delivery. Insulin independence postpartum has only been documented in two prior studies. In the first by Caplan et al. (11), 5 of 23 patients did not require additional insulin on the day of delivery. On the following 2 days, 80% of women required less than their prepregnancy dose. Information concerning prior doses of insulin, breast-feeding, or the timing of insulin recommencement was not provided in this study.

Lean et al. (13) showed a mean time to recommencement of insulin of 2.4 h (1–8 h) after vaginal delivery and 15.5 h (6–35 h) after caesarean section. Information regarding timing and magnitude of prior doses of insulin, peripartum management, and breast-feeding was not provided. It is also unclear if the caesarean section group included women who initially labored. The metabolic demands of this group differ from those undergoing an elective caesarean section. For the regression analyses, we identified three groups: vaginal delivery and caesarean section with and without prior labor. Mode of delivery did not correlate with the time to first requirement of insulin postpartum. Of note, women in this previous study were not managed with modern insulin analogs (13).

Postpartum insulin requirements could be influenced by changes in the duration of physiological action of exogenous insulin or changes in endogenous insulin production. The pharmacokinetic profile of insulin is affected by the dose,

method, and site of administration; regional blood flow (29–31); and lipohypertrophy (30). Regional blood flow is altered by exercise, massage, and vasoactive drugs. We did not find a relationship between vasodilatory agents and insulin independence. No vasoconstrictors were administered. Insulin antibodies (29) also affect insulin pharmacokinetics but are unlikely to have been significant in this study, as the frequency of antibodies in patients on insulin has fallen with the use of recombinant production and improved purification (32). Further, the presence of insulin antibodies rarely has clinical implications, and many studies show no relationship between antibodies and BGLs.

Changes in the clearance (renal or hepatic) of insulin will affect its duration of action. In pregnancy, deterioration in renal function can occur with pre-eclampsia, or progression of or de novo diabetic nephropathy. In particular, women who develop pre-eclampsia can show a transient worsening of renal function postpartum before subsequent improvement. In the current study, increased creatinine at term was associated with a longer time without insulin. Only one woman in this study developed grossly abnormal liver function tests. The role of hepatic impairment and insulin clearance could not be assessed in this study.

Finally, the pharmacodynamic duration of the action of insulin will be affected by insulin resistance. At delivery, there is a sudden reduction in insulin resistance that could prolong the pharmacological action of insulin. The temporal relationship between the change in insulin requirement and delivery of the feto-placental unit suggests that increased insulin sensitivity may be an important aetiological factor. The univariate regression analysis showed that the time from last dose of long- or intermediate-acting insulin and continuation of an infusion postpartum significantly correlated with a longer duration of time to the first dose of insulin postpartum. This suggests a role for prolongation of the pharmacodynamic action of previously administered long- or

intermediate-acting insulin. The three women on a CSII (and therefore only rapid-acting insulin) had no cessation of insulin, which suggests a role for the long- and intermediate-acting insulins. The small numbers of women managed with a CSII precluded detailed analysis of this group. Finally, the role of insulin sensitivity is supported by the relationship between increased BMI and a shorter period of insulin independence.

In our study, the duration of glucose infusion, levels of counterregulatory hormones, and residual endogenous insulin production were not assessed. The studies concerning increased endogenous insulin production in type 1 diabetes during pregnancy are discordant (33–35). As such, the effect of residual or increased β -cell function on peripartum insulin requirements warrants further consideration.

Another potential limitation of our study is the use of various insulin preparations. Most women were treated with insulin glargine; however, the long- and intermediate-acting insulin group also included insulin detemir and isophane insulin. The pharmacokinetic and pharmacodynamic properties differ, including the effect of renal impairment. Insulin detemir shows no change with renal impairment (36). The numbers of women on insulin detemir were too small for separate analysis. The effect of renal impairment on insulin glargine has not been assessed; however, dose reduction is recommended (37). Renal impairment affects the action of insulin lispro and insulin regular (31).

Recommendation of Insulin

We found considerable glucose variability postpartum with a trend to increased hypoglycemic episodes, especially after the recommencement of regular insulin. From delivery until discharge, ~94% of women had at least two BGLs <3.5 or >10.0 mmol/L and 60% had at least one hypoglycemic episode. There was an association between increased dose of insulin and out-of-range BGLs with a particular risk of hypoglycemia.

Most authors suggest that insulin be recommenced at 25–50% of pregnancy dose (16,17,19,24) or two-thirds of the

prepregnancy dose at the first meal postdelivery (17). A dose of 0.6 units/kg/day based on the postpartum weight has also been proposed (12). Other authors have used a sliding scale for short-acting insulin and commenced intermediate insulin based on postpartum weight or oral intake (4,11,22,26). These recommendations are based on experience rather than study data.

There is no policy at our institution regarding the dose of insulin to recommence postpartum. There are also no defined glycemic targets, although the primary aim is the avoidance of hypoglycemia postpartum, in accordance with guidelines published by the Australasian Diabetes in Pregnancy Society (38). Similarly, there are no published international recommendations or data concerning postpartum glycemic targets and recommencement dose of insulin. A dose of 50–60% of the prepregnancy requirement gave the fewest number of out-of-range BGLs and the least number of hypoglycemic episodes. However, 30% of women were commenced on greater than or equal to the prepregnancy dose. This appeared to be associated with increased hypoglycemia and out-of-range BGLs. In our center, larger doses of insulin were generally prescribed by clinicians who care for nonpregnant women with type 1 diabetes less frequently. There was a statistically significant relationship between the health care provider and dose of insulin prescribed and risk of hypoglycemia. This finding needs to be replicated in other centers but points to the need for those familiar with the peripartum management of women with type 1 diabetes to be involved in the prescription of insulin to ensure that all clinicians are well educated regarding the management of these women.

Breast-feeding

It is generally believed that breast-feeding further lowers the requirement for insulin (12,16) and increases the risk of hypoglycemia (12,38,39). However, this is not uniformly accepted (24). Some authors have documented a postpartum return to prepregnancy doses in 3–6 weeks, regardless of

breast-feeding (17,19,28). However, most women are advised to increase caloric intake by ~500 calories (17) or 2 kcal/kg/day (12).

In our study, the small numbers of women in the artificial feeding group precluded comparison with breast-feeding women. Reassessment of insulin requirements and risk of hypoglycemia during established breast-feeding is indicated.

In summary, we have described the peripartum management of women with type 1 diabetes at a tertiary center. Analysis of the glycemic behavior of these women suggests that changes in the pharmacodynamic profile of long- or intermediate-acting insulin may contribute to the period of apparent transient insulin independence observed in some women. The mechanism(s) underlying this change in duration of action is unknown. Finally, a dose of 50–60% of the prepregnancy requirement once insulin is recommenced in the postpartum period was associated with the lowest rate of hypoglycemia and glucose excursions. These results require validation in a larger, prospective study given that the clinical implications are significant.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.A. obtained data, conducted the statistical analysis, and wrote the manuscript. E.L.D., H.D.M., and L.C. provided intellectual input into the analytical approach and reviewed and edited the manuscript. N.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Ann Intern Med* 1998;128:517–523
2. Carron Brown S, Kyne-Grzebalski D, Mwangi B, Taylor R. Effect of management policy upon 120 type 1 diabetic pregnancies: policy decisions in practice. *Diabet Med* 1999;16:573–578
3. Curet LB, Izquierdo LA, Gilson GJ, Schneider JM, Perelman R, Converse J. Relative effects of antepartum and intrapartum maternal blood glucose levels on incidence of neonatal hypoglycemia. *J Perinatol* 1997;17:113–115
4. Miodovnik M, Mimouni F, Tsang RC, et al. Management of the insulin-dependent diabetic during labor and delivery. Influences on neonatal outcome. *Am J Perinatol* 1987;4:106–114
5. Stenninger E, Lindqvist A, Aman J, Ostlund I, Schvarcz E. Continuous Subcutaneous Glucose Monitoring System in diabetic mothers during labour and postnatal glucose adaptation of their infants. *Diabet Med* 2008;25:450–454
6. Ornoy A. Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr Endocrinol Rev* 2005;3:104–113
7. Stenninger E, Flink R, Eriksson B, Sahlén C. Long-term neurological dysfunction and neonatal hypoglycaemia after diabetic pregnancy. *Arch Dis Child Fetal Neonatal Ed* 1998;79:F174–F179
8. West TE, Lowy C. Control of blood glucose during labour in diabetic women with combined glucose and low-dose insulin infusion. *BMJ* 1977;1:1252–1254
9. Grant E, Joshi GP. Glycemic control during labor and delivery: a survey of academic centers in the United States. *Arch Gynecol Obstet* 2012;285:305–310
10. Yudkin JS, Knopfler A. Glucose and insulin infusions during labour. *Lancet* 1992;339:1479
11. Caplan RH, Pagliara AS, Beguin EA, et al. Constant intravenous insulin infusion during labor and delivery in diabetes mellitus. *Diabetes Care* 1982;5:6–10
12. Jovanovic L, Nakai Y. Successful pregnancy in women with type 1 diabetes: from preconception through postpartum care. *Endocrinol Metab Clin North Am* 2006;35:79–97, vi
13. Lean ME, Pearson DW, Sutherland HW. Insulin management during labour and delivery in mothers with diabetes. *Diabet Med* 1990;7:162–164
14. Lepercq J, Abbou H, Agostini C, et al. A standardized protocol to achieve normoglycaemia during labour and delivery in women with type 1 diabetes. *Diabetes Metab* 2008;34:33–37
15. Barrett HL, Morris J, McElduff A. Watchful waiting: a management protocol for maternal glycaemia in the peripartum period. *Aust N Z J Obstet Gynaecol* 2009;49:162–167
16. de Valk HW, Visser GH. Insulin during pregnancy, labour and delivery. *Best Pract Res Clin Obstet Gynaecol* 2011;25:65–76
17. Haigh SE, Tevaarwerk GJ, Harding PE, Hurst C. A method for maintaining normoglycemia during labour and delivery in insulin-dependent diabetic women. *Can Med Assoc J* 1982;126:487–490
18. Rosenberg VA, Eglington GS, Rauch ER, Skupski DW. Intrapartum maternal glycemic control in women with insulin requiring diabetes: a randomized clinical trial of rotating fluids versus insulin drip. *Am J Obstet Gynecol* 2006;195:1095–1099
19. Hanson U, Moberg P, Efendic S. Dosage of insulin during delivery and the immediate post-partum period in pregnant diabetics. *Acta Obstet Gynecol Scand* 1981;60:183–186
20. Soler NG, Malins JM. Diabetic pregnancy: management of diabetes on the day of delivery. *Diabetologia* 1978;15:441–446
21. Golde SH, Good-Anderson B, Montoro M, Artal R. Insulin requirements during labor: a reappraisal. *Am J Obstet Gynecol* 1982;144:556–559
22. Feldberg D, Dicker D, Samuel N, Peleg D, Karp M, Goldman JA. Intrapartum management of insulin-dependent diabetes mellitus (IDDM) gestants. A comparative study of constant intravenous insulin infusion and continuous subcutaneous insulin infusion pump (CSII). *Acta Obstet Gynecol Scand* 1988;67:333–338
23. Jovanovic L, Peterson CM. Insulin and glucose requirements during the first stage of labor in insulin-dependent diabetic women. *Am J Med* 1983;75:607–612
24. Crombach G, Siebolds M, Mies R. Insulin use in pregnancy. Clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1993;24:89–100
25. Maheux PC, Bonin B, Dizazo A, et al. Glucose homeostasis during spontaneous labor in normal human pregnancy. *J Clin Endocrinol Metab* 1996;81:209–215
26. Kjos SL. Postpartum care of the woman with diabetes. *Clin Obstet Gynecol* 2000;43:75–86
27. Njenga E, Lind T, Taylor R. Five year audit of peripartum blood glucose control in type 1 diabetic patients. *Diabet Med* 1992;9:567–570
28. Hare JW. Insulin management of type I and type II diabetes in pregnancy. *Clin Obstet Gynecol* 1991;34:494–504
29. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. *Diabetes Care* 1984;7:188–199
30. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab* 2012;14:780–788
31. Morello CM. Pharmacokinetics and pharmacodynamics of insulin analogs in special populations with type 2 diabetes mellitus. *Int J Gen Med* 2011;4:827–835
32. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993;16(Suppl. 3):155–165
33. Ilic S, Jovanovic L, Wollitzer AO. Is the paradoxical first trimester drop in insulin requirement due to an increase in C-peptide concentration in pregnant type I diabetic women? *Diabetologia* 2000;43:1329–1330

34. Murphy HR, Elleri D, Allen JM, Simmons D, Nodale M, Hovorka R. Plasma C-peptide concentration in women with type 1 diabetes during early and late pregnancy. *Diabet Med* 2012;29:e361–e364
35. Nielsen LR, Rehfeld JF, Pedersen-Bjergaard U, Damm P, Mathiesen ER. Pregnancy-induced rise in serum C-peptide concentrations in women with type 1 diabetes. *Diabetes Care* 2009;32:1052–1057
36. Nordisk, N. Levemir (insulin detemir [rDNA origin] injection) (prescribing information), 2010. Available from www.novo-pi.com/levemir.pdf. Accessed 5 October 2013
37. Sanofi. Lantus (insulin glargine [rDNA origin] injection) (prescribing information), 2007. Available from <http://productions.sanofi.us/lantus/lantus.html>. Accessed 5 October 2013
38. McElduff A, Cheung NW, McIntyre HD, et al.; Australasian Diabetes in Pregnancy Society. The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy. *Med J Aust* 2005;183:373–377
39. Davison JM, Hytten FE. The effect of pregnancy on the renal handling of glucose. *Br J Obstet Gynaecol* 1975;82:374–381