Title: Intravenous Insulin vs. Subcutaneous Insulin Infusion in Intrapartum Management of Type 1 Diabetes Mellitus

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Study Protocol/Methods

We conducted a randomized clinical trial at a single tertiary care center in central Massachusetts from March 2021 until April 2023. Prior to study initiation, approval was obtained from the University of Massachusetts Chan Medical School institutional review board. Written informed consent was obtained from all participants before enrollment and patient safety data and trial progress was assessed via a Data Safety Monitoring Board with all reporting following Consolidated Standard of Reporting Trials guidelines.

Inclusion criteria included pregnant patients aged 18 years or older with a known diagnosis of T1DM that were managed with CSII/insulin pump. All included participants had to obtain pregnancy and delivery care the study institution and had to be able to provide written informed consent in English or Spanish. Patients were not eligible if they were under the age of 18 years old, had multiple gestations, had altered state of consciousness intrapartum, were critically ill requiring intensive care unit admission, at risk for suicide, presented with diabetic ketoacidosis on admission for delivery, had an intrauterine fetal demise prior to labor, fetal anomalies, or if the participant was unable to partake in their own care.

All eligible participants were approached antenatally during routine prenatal care and consented for participation. Participants were then randomly allocated to either continuation of an intrapartum CSII/insulin pump or intravenous insulin infusion. Permutated block randomization with varying blocks sizes was used to stratify randomization by intrapartum glycemic management strategy (CSII vs. IV). The resulting group allocations were kept in sealed, opaque envelopes until opened by the provider at the time of randomization. Patients and providers were not blinded to randomization given active participation of providers and patients was needed in both study arms. Once admitted for labor, two separate intrapartum glycemic protocols were followed based on randomization category (Supplementary Figures 1 and 2).

All medical records were reviewed for maternal demographics, clinical characteristics, and perinatal outcomes including primary and secondary outcomes. The primary outcome for the study was the first neonatal blood glucose level measured after birth. At our institution, it is policy that all neonates of mothers diagnosed with pre-gestational diabetes receive a heel-stick glucose measurement within the first 2 hours of life. Neonatal hypoglycemia was defined as blood glucose level less than 40 mg/dL, which prompts treatment and further monitoring at our study institution.[18] In order to detect a 10 mg/dL difference in mean neonatal blood glucose levels between groups with a type 1 alpha error of 0.05 and 80% power with equal group sizes, 35 participants in each group were needed for a total sample size of 70 patients.

Secondary neonatal outcomes included mean neonatal glucose in the first 24 hours of life, neonatal hyperglycemia treatments including oral or intravenous treatment, 5 minute APGAR less than 7, NICU admission, neonatal birthweight, neonatal birthweight meeting large for gestational age criteria by Fenton growth calculator for preterm infants or World Health Organization growth calculator for term infants, or additional adverse neonatal outcomes including respiratory distress requiring intubation or continuous positive airway pressure (CPAP), hyperbilirubinemia, and neonatal cooling. Maternal secondary outcomes included intrapartum hypoglycemic events defined as blood glucose less than 60 mg/dL, intrapartum severe maternal hyperglycemic events defined as blood glucose greater than 200 mg/dL, development of diabetic ketoacidosis intrapartum, mode of delivery, shoulder dystocia at delivery, development of gestational hypertension or pre-eclampsia, maternal blood transfusion, and maternal intensive care unit admission.

All summary data were collected and managed using REDCap tools hosted at UMASS Chan Medical School. Summary data are reported as frequencies for categorical variables and

mean (standard deviation) or median (interquartile range) for continuous variables. All categorical variables were compared using Fisher exact test and Chi square testing where appropriate, while continuous variables were assessed for normality and t-tests or Wilcoxon rank sum tests were used where appropriate. For all analyses, a two-sided significance level of $P<0.05$ was considered statistically significant. Analyses were performed using STATA/SE 17.0 (StataCorp, College Station, TX).