Factors Associated With Hypoglycemia Among Neonates Born to Mothers With Gestational Diabetes Mellitus

Martha B. Kole,[1] Nina K. Ayala,[1] Melissa A. Clark,[2] Phinnara Has,[1] Mathew Esposito,[1] and Erika F. Werner[1]

Diabetes Care 2020;43:e194–e195 | https://doi.org/10.2337/dc20-1261

Among women with gestational diabetes mellitus (GDM), hyperinsulinemic hypoglycemia of the neonate is a common complication because the hyperglycemic intrauterine environment leads to a relative increase in fetal insulin secretion (1). After delivery, persistent insulin elevation results in neonatal hypoglycemia that can be identified by clinical symptoms or routine screening. Exposure to GDM and hyperinsulinemic hypoglycemia have been associated with neurological sequelae and poor neurodevelopmental outcomes (1) as well as long-term metabolic abnormalities including type 2 diabetes and childhood obesity (2). Despite the morbidity associated with neonatal hypoglycemia, there is a paucity of data on predictors of the condition. The goal of this secondary analysis was to evaluate pregnancy characteristics among neonates who developed hypoglycemia within the first 24 h of life compared with those who did not.

The prospective cohort study was performed at a single academic medical center between January 2016 and June 2018. Women included were ≥18 years old, diagnosed with GDM during their pregnancy, and enrolled during their postpartum hospitalization. Following enrollment, demographic, obstetric, and neonatal data were obtained from the electronic medical record.

Included in this analysis were 597 pregnancies among which 234 neonates (39%) had hypoglycemia and 363 neonates (61%) did not. Among all pregnancies, 50% had GDM management by diet alone, 36% insulin, 11% glyburide, 0.2% metformin, and 1.2% insulin in combination with an oral agent. Characteristics of women whose neonates had hypoglycemia did not differ by age, parity, socioeconomic status, family, or personal history of diabetes in comparison with those who did not have neonates with hypoglycemia. However, mothers of neonates with hypoglycemia had a higher mean BMI at the initial prenatal visit (32.6 vs. 31.8 kg/m^2, $P = 0.04$). There were also no differences in maternal weight gain, induction of labor, insulin use during labor, highest maternal blood glucose level in labor, or mode of delivery between groups.

Neonatal hypoglycemia occurred in 35% of pregnancies managed with diet alone, 43% with insulin alone, and 52% with glyburide. Medical management compared with dietary management was associated with an increased risk of neonatal hypoglycemia (Table 1). However, when individual medical therapies were compared with dietary management, only glyburide was associated with an increased risk in unadjusted analyses. After adjustment for significant covariates, glyburide continued to be associated with an increased risk of neonatal hypoglycemia (Table 1).

When neonatal factors were evaluated as risk factors for hypoglycemia, neonates born preterm compared with

Table 1—Unadjusted and adjusted RR of neonatal hypoglycemia in women with GDM

	RR (95% CI)	Adjusted RR (95%CI)
BMI at initial prenatal visit ≥30 kg/m^2	1.13 (0.97, 1.31)	1.09 (0.94, 1.26)†
Gestational age at delivery <37 weeks	1.55 (1.06, 2.28)	1.50 (1.01, 2.22)‡
GDM management		
Any medication	1.20 (1.02, 1.41)	1.15 (0.99, 1.33)*
Insulin only	1.23 (0.99, 1.54)	1.17 (0.95, 1.44)*
Glyburide only	1.71 (1.15, 2.54)	1.61 (1.08, 2.39)*

†Adjustment for gestational age at delivery and any GDM medication. ‡Adjustment for BMI at initial prenatal visit and any GDM medication. *Adjustment for gestational age at delivery and BMI at initial prenatal visit.

[1]*Division of Maternal Fetal Medicine, Women and Infants Hospital, Alpert Medical School of Brown University, Providence, RI*
[2]*Department of Health Services, Policy and Practice, Brown University School of Public Health, and Department of Obstetrics and Gynecology, Women and Infants Hospital, Alpert Medical School of Brown University, Providence, RI*

Corresponding author: Martha B. Kole, mkole@wihri.org

Received 26 May 2020 and accepted 1 September 2020

term were more likely to have hypoglycemia (Table 1). This association persisted after adjustment for significant covariates. Neither being born large for gestational age nor being born small for gestational age was associated with an increased risk of neonatal hypoglycemia (relative risk [RR] 1.29 [95% CI 0.84, 2.02] and RR 0.88 [95% CI 0.44, 1.76], respectively). There were no differences in Apgar score or birth weight between hypoglycemic neonates and euglycemic neonates, but those with hypoglycemia were more likely to be admitted to the neonatal intensive care unit (RR 2.48 [95% CI 1.80, 3.42]).

The strengths of this study are its large size and racially and economically diverse population. It is limited by the observational nature of the data and being performed at a single study site. These results are consistent with previous studies demonstrating no difference in neonatal hypoglycemia among mothers treated with insulin compared with those not using insulin (3), increased risk of hypoglycemia in women treated with glyburide (4), and an increased risk of neonatal hypoglycemia in those delivered at an earlier gestational age (5).

In conclusion, we found that neonates had a significantly higher risk of hypoglycemia if their mother used glyburide for treatment of GDM or they were born preterm. We did not find a difference in neonatal hypoglycemia risk between pregnancies that required insulin and those managed with dietary modifications only. Importantly, this study highlights the importance of universal neonatal screening for hypoglycemia following pregnancies with GDM. While 39% of women with GDM had a neonate with hypoglycemia, even women traditionally considered "lower risk" still had a relatively high incidence of neonatal hypoglycemia: hypoglycemia was observed in 35% of the neonates of women with GDM managed by diet alone and 33% born after 39 weeks. Due to the short- and long-term implications of neonatal hypoglycemia, increasing incidence of GDM, relatively low cost of screening, and difficulty identifying "at risk" neonates, we believe universal glucose screening for all neonates born to mothers with GDM is prudent. We also believe that women should be counseled that glyburide use may be associated with an increased risk of neonatal hypoglycemia prior to starting the medication.

Funding. Work for this project was supported by American Diabetes Association grant 1-16-ICTS-118 and the Hassenfeld Child Health Innovations Institute.

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

Author Contributions. M.B.K. was responsible for study design, data abstraction, and data interpretation as well as composing and editing the manuscript. N.K.A. was responsible for study design, data abstraction, and data interpretation as well as composing and editing the manuscript. M.A.C. was responsible for study design, data interpretation, and editing the manuscript. P.H. was responsible for study design, statistical analysis, and data interpretation. M.E. was responsible for data interpretation and editing the manuscript. E.F.W. was responsible for study design, data interpretation, and editing the manuscript. M.B.K. 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.

Prior Presentation. Parts of this study were presented in abstract form at the Society of Maternal-Fetal Medicine 40th Annual Pregnancy Meeting, Grapevine, TX, 3–8 February 2020.

References

1. Güemes M, Hussain K. Hyperinsulinemic hypoglycemia. Pediatr Clin North Am 2015;62:1017–1036

2. Blotsky AL, Rahme E, Dahhou M, Nakhla M, Dasgupta K. Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. CMAJ 2019;191:E410–E417

3. Voormolen DN, de Wit L, van Rijn BB, et al. Neonatal hypoglycemia following diet-controlled and insulin-treated gestational diabetes mellitus. Diabetes Care 2018;41:1385–1390

4. Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131:e49–e64

5. DePuy AM, Coassolo KM, Som DA, Smulian JC. Neonatal hypoglycemia in term, nondiabetic pregnancies. Am J Obstet Gynecol 2009;200:e45–e51