AACE Clinical Case Rep. 10 (2024) 224–228

Clinical Case Reports™
www.aaceclinicalcasereports.com

Case Report

# Management of Dysglycemia in a Pregnancy Complicated by Fanconi–Bickel Syndrome

Emily D. Szmuilowicz, MD, MS [1, *], Ellen Fruzyna, BS [1], Nigel Madden, MD [2], Janelle R. Bolden, MD [2], Anne Kozek, RD [3], Erika Vucko, APRN-NP, FNP [3], Cybele Ghossein, MD [4], Grant Barish, MD [1, 5]

[1] *Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois*
[2] *Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois*
[3] *Division of Pediatric Genetics, Genomics and Metabolism, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois*
[4] *Division of Nephrology and Hypertension, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois*
[5] *Division of Endocrinology, Diabetes, and Metabolism, Jesse Brown VA Medical Center, Chicago, Illinois*

ARTICLE INFO

*Article history:*
Received 17 April 2024
Received in revised form
10 July 2024
Accepted 23 July 2024
Available online 27 July 2024

*Key words:*
Fanconi–Bickel Syndrome
pregnancy
glucose transporter 2
continuous glucose monitoring
cornstarch therapy

ABSTRACT

*Background/Objective:* Fanconi–Bickel Syndrome (FBS) is an inherited disorder of glucose metabolism resulting from functional loss of glucose transporter 2 characterized by fasting hypoglycemia oscillating with postprandial hyperglycemia. Dysglycemia treatment strategies during FBS pregnancy have not been reported, and insulin therapy carries significant risk due to fasting hypoglycemia in FBS. We report for the first time: (1) glycemic profiles obtained via continuous glucose monitoring (CGM), (2) CGM-guided strategies for cornstarch and nutritional therapy for fasting hypoglycemia and postprandial hyperglycemia, respectively, and (3) placental glucose transporter 2 isoform expression in a pregnant individual with FBS.

*Case Report:* A 27-year-old woman with FBS presented at 6 weeks gestation for management of fasting hypoglycemia and postprandial hyperglycemia. Cornstarch therapy for fasting hypoglycemia and nutritional therapy for postprandial hyperglycemia were iteratively adjusted across gestation based on CGM-derived glycemic patterns. Pregnancy-specific glycemic targets were successfully achieved, and she delivered a healthy term infant. Glucose transporter 2 isoform was not detected in placental tissue.

*Discussion:* We report for the first time glycemic patterns across gestation in a pregnant individual with FBS. Glycemic targets were achieved through stepwise optimization of nutritional and cornstarch therapy, both guided by CGM data. Our approach obviated the need for insulin therapy, which carries amplified risk in FBS.

*Conclusion:* Fasting hypoglycemia and postprandial hyperglycemia can be effectively treated through CGM-guided adjustment of both nutritional and glucose polymer therapies in FBS pregnancy. More broadly, our case highlights a novel application for CGM in the management of uncommon glucose metabolism disorders during pregnancy.



## Introduction

Fanconi–Bickel Syndrome (FBS) is an inherited disorder with autosomal recessive inheritance characterized by functional loss of glucose transporter 2 (GLUT2), a facilitative glucose transporter found in multiple tissues including hepatocytes, pancreatic beta cells, renal tubular cells, and intestinal epithelial cells.[1,2] Functional loss of GLUT2 leads to a distinctive pattern of dysglycemia

*Abbreviations:* CGM, continuous glucose monitoring; FBS, Fanconi–Bickel syndrome; GLUT, glucose transporter; MNT, medical nutrition therapy; TIR, time in range.

Informed Consent: Informed consent was obtained from the patient.

* Address correspondence to Dr Emily D. Szmuilowicz, Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, 645 N. MI Ave, Suite 530, Chicago, Illinois.
*E-mail address:* edszmuilowicz@northwestern.edu (E.D. Szmuilowicz).

https://doi.org/10.1016/j.aace.2024.07.008

characterized by (1) postprandial hyperglycemia due to decreased utilization of glucose in the postprandial state resulting from impaired monosaccharide uptake by the liver, possibly enhanced by impaired pancreatic insulin secretion; and (2) fasting hypoglycemia due to impaired glucose mobilization from the liver that is augmented by renal glucose loss.[1-4] Affected individuals additionally manifest proximal renal tubular dysfunction and profound short stature.[1] General clinical management strategies for FBS include "frequent small meals"[3,4] and overnight uncooked cornstarch,[4] a glucose polymer that is broken down slowly, to ameliorate fasting hypoglycemia. However, specific guidance for treatment of FBS-associated dysglycemia has not been reported, including during pregnancy.

Optimal glycemia during pregnancy is of paramount importance, given the increased risk of adverse pregnancy outcomes with poor glycemic control including hypertensive disorders of pregnancy, cesarean birth, miscarriage/stillbirth, fetal growth disturbance, preterm delivery, neonatal hypoglycemia, respiratory complications, and neonatal intensive care unit admission.[5] These risks are substantially decreased with optimal glycemic control,[6] and glycemic targets for pregnant individuals with type 1 or type 2 diabetes[6] are shown in Table 1. Clinical management of FBS-associated dysglycemia during pregnancy presents unique challenges because of the following: (1) glycemic patterns in pregnancy affected by FBS have not been reported; (2) specific guidance for cornstarch therapy and medical nutrition therapy (MNT) for treatment of FBS-associated dysglycemia has not been described; and (3) due to the elevated fasting hypoglycemia risk, avoidance of insulin therapy (the standard medical therapy for hyperglycemia during pregnancy[6]) is recommended in FBS.[4]

The objectives of this report are to describe for the first time (1) glycemic profiles obtained via CGM; (2) CGM-guided specific management strategies for treatment of both fasting hypoglycemia and postprandial hyperglycemia; and (3) placental GLUT isoform expression in a pregnant individual with FBS.

## Case Report

A 27-year-old woman with FBS presented at 6 weeks gestation for management of dysglycemia during pregnancy. Pregnancy history was notable for a miscarriage at age 22, and a term cesarean delivery at age 23 (birth weight 3.16 kg). During her previous pregnancy, overnight tube feeds to treat hypoglycemia were complicated by gastrointestinal adverse effects and postprandial hyperglycemia; prandial insulin therapy was considered but never started due to hypoglycemia risk. Diagnostic CGM performed once during prior pregnancy revealed postprandial hyperglycemia and overnight hypoglycemia with hypoglycemia unawareness. Past medical history included proximal renal tubular acidosis complicated by hypophosphatemia and hypokalemia, and rickets with osteomalacia. Physical examination was notable for profound short stature (height 116.8 cm [3' 10"]) and weight 43.4 kg (96 lb). Hemoglobin A1c (HbA1c) on presentation was 5.9%, consistent with the mild hemoglobin A1c elevations previously reported in FBS,[4,7] presumably reflecting alternating periods of hypoglycemia and hyperglycemia. Periodic blood glucose monitoring showed marked variability, ranging from 38 mg/dL in the fasting state overnight to above 400 mg/dL postprandially. CGM (Dexcom G6, San Diego, California) was initiated at 7 weeks gestation, showing time in range (TIR) of 52% (Fig. 1*A*), below the goal of >70% time in the pregnancy-specific target range of 63-140 mg/dL recommended for pregnant individuals with pregestational type 1 diabetes.[6] Defensive carbohydrate intake, which was consumed to prevent fasting hypoglycemia, led to postprandial hyperglycemia and glycemic variability.

Long-acting uncooked cornstarch therapy (Glycosade, Vitaflo) to ameliorate fasting hypoglycemia and MNT aimed at amelioration of postprandial hyperglycemia were initiated (Table 2). By 17 weeks gestation, she achieved TIR >70% (Fig. 1*B*), with improvement in both fasting hypoglycemia and postprandial hyperglycemia. Throughout gestation, serial adjustments to long-acting and/or short-acting cornstarch therapy and MNT were performed iteratively based on CGM trends (Table 2). She was largely able to maintain TIR >70%, except for transient periods of postprandial hyperglycemia that improved with iterative nutritional adjustments guided by patient- and provider-observed glycemic response on CGM. By 33 weeks gestation, premeal hypoglycemia emerged at the end of the cornstarch dosing interval. Co-administration of whole milk as a source of fat and protein together with cornstarch therapy, to prolong its duration of action, enabled achievement of 84% TIR by 35 weeks gestation and 79% TIR by 37 weeks gestation. Total weight gain during pregnancy was 18 lb (8.2 kg), which was within the target range for her body mass index.

She underwent uncomplicated cesarean delivery at 38 weeks 2 days gestation, delivering a healthy female infant weighing 3.45 kg (7 lb 9.7 oz). The neonate had a brief neonatal intensive care unit admission for hypoglycemia requiring treatment with glucose gel but otherwise did well and was discharged home on postoperative day 3. Approval was obtained from the institutional review board to perform placenta sn-RNA seq preparation and analysis. Nuclei were isolated from 100 mg of placenta preserved in RNAlater (ThermoFisher) using a protocol adapted from Mas et al.[8] Libraries were prepared using Chromium single cell 3' reagent kit (10x Genomics) and sequenced on NovaSeq X (Illumina). Reads were aligned to the reference genome (GRCh38) using Cell Ranger (v6.1.2). Seurat

**Table 1**
Recommended Glucose Targets for Pregnant People with Pre-existing Diabetes (American Diabetes Association)

| | |
|---|---|
| Fasting glucose | 70–95 mg/dL (3.9–5.3 mmol/L) and either |
| One-hour postprandial glucose | 110–140 mg/dL (6.1–7.8 mmol/L) or |
| Two-hour postprandial glucose | 100–120 mg/dL (5.6–6.7 mmol/L) |

### Highlights

- Fanconi–Bickel Syndrome (FBS) leads to dysglycemia.
- Dysglycemia treatment strategies during FBS pregnancy have not been reported.
- Insulin therapy carries significant risk in FBS due to fasting hypoglycemia.
- Continuous glucose monitoring allows targeted nutrition and cornstarch therapy.
- Our treatment approach obviated the need for insulin therapy.

### Clinical Relevance

We report for the first time glucose trends, cornstarch and nutritional strategies for treatment of dysglycemia, and placental glucose transporter 2 expression in a pregnancy complicated by Fanconi–Bickel Syndrome. Our case highlights a novel application for continuous glucose monitoring in managing uncommon glucose metabolism disorders during pregnancy.

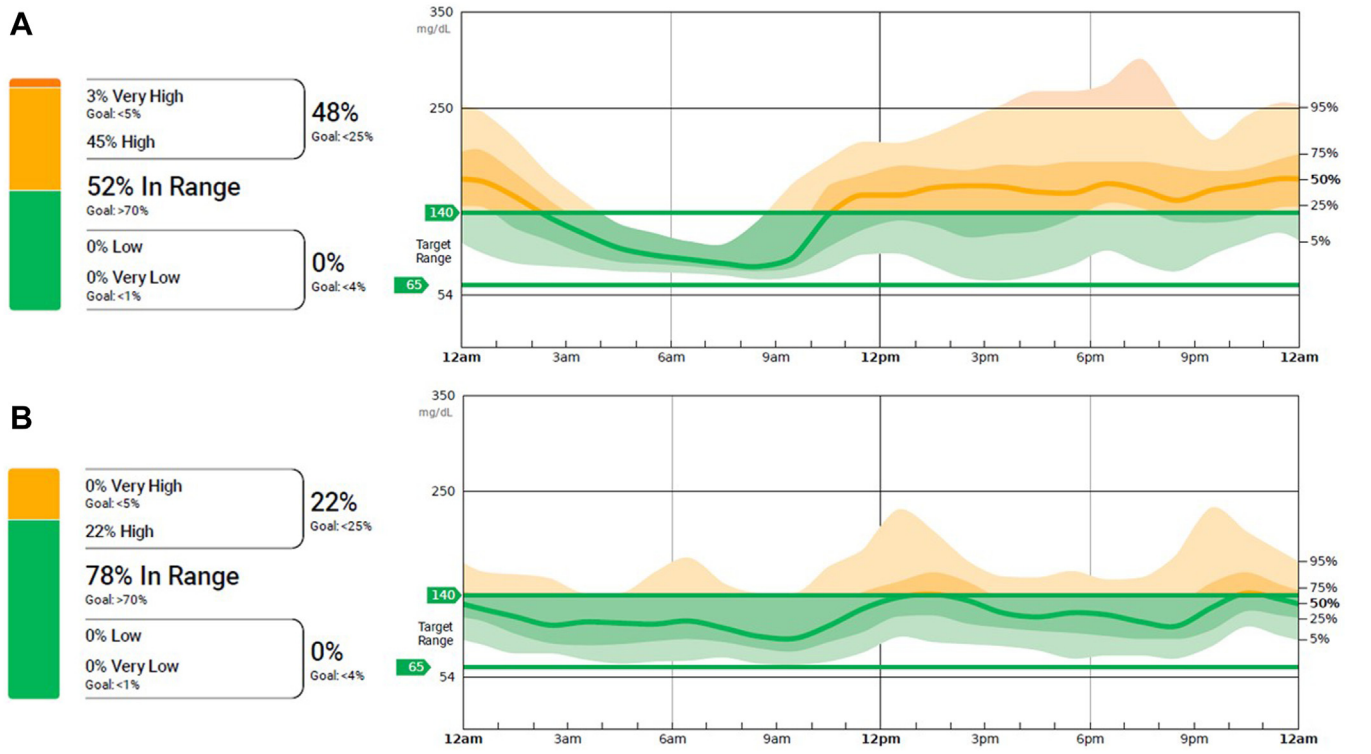


**Fig. 1.** Continuous glucose monitoring data from a pregnant individual with Fanconi–Bickel Syndrome in the first trimester (7 weeks gestation; *A*) and second trimester (17 weeks gestation; *B*). By convention during pregnancy,[6] glucose target range was defined as 65-140 mg/dL (the lower limit of the target range is set to 65 mg/dL instead of 63 mg/dL when 5 mg/dL is the minimum increment available on the software program). Standard goal for % time in range is >70% for type 1 diabetes pregnancy (noting that the recommended goals during pregnancy for time spent in target ranges were not specified for pregestational type 2 diabetes or gestational diabetes due to insufficient data[6]). Fourteen days of glucose data are displayed by convention as the Ambulatory Glucose Profile (AGP). At 7 weeks gestation (*A*), the patient had 52% time in range. At 17 weeks gestation (*B*), the patient had 78% time in range.

**Table 2**
Key Modifications to Cornstarch Dosing in a Pregnant Individual with Fanconi–Bickel Syndrome

| GA | Long-acting cornstarch (Glycosade)/liquid | Short-acting cornstarch (Argo) dose | Glucose trends noted | Therapeutic adjustment made |
|---|---|---|---|---|
| 8 | None | None | Intermittent hypoglycemia (30-40 mg/dL) overnight and early morning | Added 60 g Glycosade at bedtime |
| 9 | 60 g at bedtime in water | None | Hypoglycemia in early morning | Bedtime Glycosade increased to 75 g and then 90 g at bedtime |
| 13 | 90 g at bedtime in water | none | Hypoglycemia before waking (5–6 am)<br>Some premeal hypoglycemia during the day | Increased bedtime/overnight Glycosade dose<br>Snack with fat and protein added to bedtime Glycosade to prolong duration of action<br>Argo added mid-morning and mid-afternoon |
| 17-18 | 120 g at bedtime and 30 g at 4 AM in water | 8 g at 10 AM and 4 PM | Glycemic targets achieved | No changes |
| 20 | 120 g at bedtime and 30 g at 4 AM in water | 8 g at 10 AM and 4 PM | Overnight hyperglycemia | Bedtime Glycosade dose decreased |
| 28 | 90 g at bedtime and 30 g at 3 AM in water | 8 g at 10 AM and 4 PM | Early overnight hyperglycemia and late overnight hypoglycemia | Changed Glycosade to 60 g at bedtime and 60 g at 2 AM<br>Subsequently changed to 30 g at bedtime and 30 g at 3 AM for overnight hyperglycemia |
| 29 | 30 g at bedtime and 30 g at 3 AM in water | 8 g at 10 AM and 4 PM | Hyperglycemia overnight and postmeals<br>Argo being taken with 10 AM meal rather than as mid-morning snack | Decreased Glycosade to 20 g at bedtime and 20 g at 3 AM<br>Discontinued Argo at 10 AM<br>Discontinued Argo at 4 PM unless dinner will be consumed after 6 PM |
| 30 | 20 g at bedtime and 20 g at 3 AM in water | Only taken if dinner eaten later than 6 PM | Initially glycemic targets achieved then overnight hypoglycemia | Increased to 20 g at 9 PM, 1 AM, and 5 AM |
| 33 | 20 g at 9 PM, 1 AM, and 5 AM in water | None | Intermittent hypoglycemia 2-3 h after Glycosade administration | 4 oz lactose-free whole milk added to Glycosade to add protein/fat to promote slower digestion |
| 35 | 20 g at 9 PM, 1 AM and 5 AM in lactose-free whole milk | None | Overnight hyperglycemia | Glycosade dose decreased and 5 AM Glycosade discontinued<br>9 PM and 1 AM Glycosade doses continued to be mixed in lactose-free whole milk to promote slower digestion |

Abbreviations: GA = gestational age.

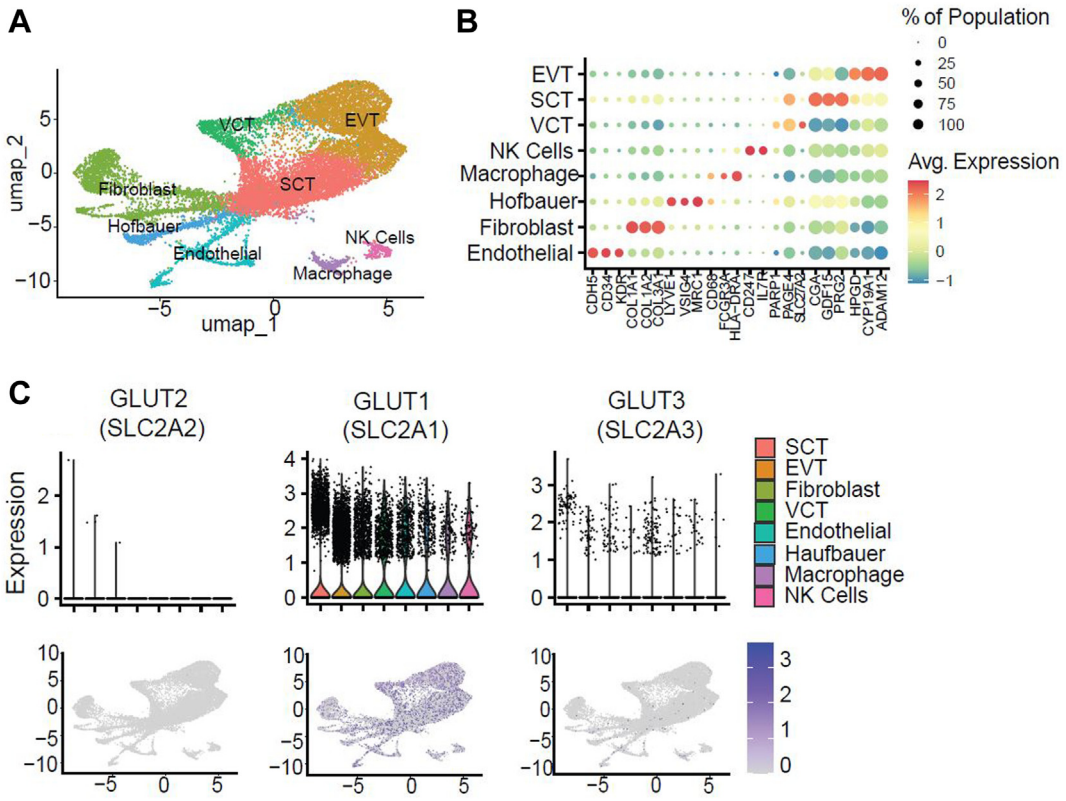


**Fig. 2.** Single-nuclear RNA-seq of placenta from patient with Fanconi–Bickel syndrome reveals no GLUT2 expression in any placenta subpopulations *A*. UMAP (Uniform manifold approximation and projection) plot of placenta nuclei subpopulations, colored by cell identity. UMAP clusters were identified from high-quality nuclei (200–2500 features, <5% mitochondrial counts) using Seurat's "FindNeighbors," "FindClusters," and "RunUMAP" functions with $n = 13$ dimensions. Cell type identities were assigned to each cluster by examining expression of known lineage-specific marker genes.[9-11] *B*. Dot-plot of selected placenta lineage marker genes in all populations *C*. Violin plots (*Top*) and feature plots (*bottom*) of GLUT2, GLUT1 and GLUT3 expression in all placenta populations. *GLUT* = glucose transporter 2; *EVT* = extravillous trophoblast; *SCT* = synctiotrophoblast; *VCT* = villous cytotrophoblast.

v5.0.2 was utilized to perform guided clustering analysis and examine cluster-specific GLUT isoform expression. GLUT2 (SLC2A2) was not detected in any placenta subpopulations, while GLUT1 (SLC2A1) was expressed at high levels and GLUT3 at more modest levels (Fig. 2*C*).

## Discussion

For the first time we report glucose data, including CGM-derived glycemic patterns, in a pregnant individual with FBS, an inherited disorder of glucose metabolism resulting from functional loss of GLUT2 characterized by fasting hypoglycemia oscillating with postprandial hyperglycemia.[1,2] While FBS is rare, the unique glycemic profile of FBS amplifies, via distinct pathophysiologic mechanisms, the glycemic patterns commonly observed during pregnancy. During pregnancy, a universal progressive rise in insulin resistance facilitates increased glucose availability for the developing fetus while decreased fasting glucose concentrations are observed due to both volume expansion in early pregnancy and augmented fetoplacental glucose utilization in late pregnancy,[12] a metabolic pattern classically termed "accelerated starvation and facilitated anabolism."[9] Since insulin use carries uniquely increased hypoglycemia risk in FBS, optimization of nutritional therapy that may obviate the need for insulin therapy is all the more essential. Furthermore, risks of maternal hyperglycemia and resultant increased fetal gestational weight gain are potentially heightened in this mother with profound short stature.

Achieving glycemic targets is crucial during pregnancy,[6] as maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia via GLUT-mediated transplacental glucose diffusion,[10] increasing risk of fetal and maternal complications.[5,6] Over 14 unique GLUT2 (SLC2A2) variants have been linked to FBS,[11] resulting in varying loss of function effects on transport and expression levels when examined in vitro.[13] The most well--characterized placental GLUT is GLUT1 (SLC2A1), which is widely distributed throughout the placenta.[14-17] GLUT3 has intermediate placental expression, and other isoforms including GLUT4, GLUT9, and GLUT12 have been observed at low levels.[10] Critically, GLUT2 (SLC2A2) transcript and protein have not been detected in preterm or term placenta.[18,19] We examined placental GLUT isoform expression to assess whether placental GLUT expression and distribution deviated from expected patterns, as dysfunctional GLUT2-mediated maternofetal placental glucose transport could potentially lessen transplacental glucose transport and mitigate fetal hyperglycemia. However, consistent with previously reported patterns, GLUT2 (SLC2A2) was not detected in any placenta subpopulations (Fig. 2*C*), suggesting that functional loss of GLUT2 does not differentially impact maternofetal glucose transport and that conventional hyperglycemia treatment strategies should be employed in FBS.

No guidance currently exists describing specific nutritional or cornstarch treatment strategies for FBS-associated dysglycemia in pregnancy, and the fasting hypoglycemia characteristic of FBS presents unique safety concerns with exogenous insulin use.[1,4] One successful pregnancy in a woman with FBS who had

gestational diabetes was reported,[7] but glucose data and specific treatment strategies were not available. CGM use, a cornerstone of modern diabetes management,[6] has not previously been described in FBS.

In this case, we achieved conventional pregnancy CGM targets through (1) stepwise adjustments of cornstarch therapy, and (2) optimization of MNT strategies, both iteratively guided by CGM trends. At varying points of gestation, CGM data revealed postprandial hyperglycemia and varying patterns of overnight hypo- and hyperglycemia despite implementation of the recommended "frequent small meals" and cornstarch therapy,[3,4] glycemic patterns that would likely have been unrecognized without CGM use. CGM-guided modifications to meal composition, including pairing protein intake with both mealtime carbohydrate and cornstarch intake and substitution of high- for low-glycemic index carbohydrates, were effective in ameliorating even severe postprandial hyperglycemia (intermittently greater than 400 mg/dL at presentation). Importantly, our treatment approach obviated the need for insulin therapy, which carries uniquely amplified risk in FBS and in the setting of hypoglycemia unawareness, which significantly increases risk of severe hypoglycemic events.[20] While FBS is rare, we provide the first description for other clinicians caring for pregnant individuals with FBS successful dysglycemia monitoring and treatment strategies. Additionally, our report more broadly illustrates how both conventional MNT and infrequently-used glucose polymer therapies can be successfully tailored to CGM-derived glycemic patterns, highlighting a novel application for CGM in the management of uncommon glucose metabolism disorders during pregnancy.

## Disclosure

Dr Cybele Ghossein serves on the scientific advisory board for Horizon (Amgen).

## Acknowledgment

G. B. was funded by Merit Review Award #I01BX004898 from the United States (U.S.) Department of Veterans Affairs and National Institutes of Health (NIH) grant R01DK108987. E. F. was funded by NIH T32 GM008061. The article contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

## References

1. OMIM® - Online mendelian inheritance in Man®. # 227810 FANCONI-BICKEL SYNDROME. Accessed March 11, 2024. https://www.omim.org/entry/227810
2. Sharari S, Abou-Alloul M, Hussain K, Ahmad Khan F. Fanconi-bickel syndrome: a review of the mechanisms that lead to dysglycaemia. *Int J Mol Sci*. 2020;21(17):6286. https://doi.org/10.3390/ijms21176286
3. Manz F, Bickel H, Brodehl J, et al. Fanconi-Bickel syndrome. *Pediatr Nephrol*. 1987;1(3):509–518. https://doi.org/10.1007/BF00849262
4. Taha D, Al-Harbi N, Al-Sabban E. Hyperglycemia and hypoinsulinemia in patients with Fanconi-Bickel syndrome. *J Pediatr Endocrinol Metab*. 2008;21(6):581–586.
5. American College of Obstetricians Gynecologists' Committee on Practice Bulletins. ACOG practice bulletin No. 201: pregestational diabetes mellitus. *Obstet Gynecol*. 2018;132(6):e228–e248. https://doi.org/10.1097/AOG.0000000000002960
6. American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Supplement_1):S282–S294. https://doi.org/10.2337/dc24-S015
7. Pena L, Charrow J. Fanconi-Bickel syndrome: report of life history and successful pregnancy in an affected patient. *Am J Med Genet*. 2011;155A(2):415–417. https://doi.org/10.1002/ajmg.a.33822
8. Rousselle TV, McDaniels JM, Shetty AC, Bardhi E, Maluf DG, Mas VR. An optimized protocol for single nuclei isolation from clinical biopsies for RNA-seq. *Sci Rep*. 2022;12(1):9851. https://doi.org/10.1038/s41598-022-14099-9
9. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*. 1980;29(12):1023–1035.
10. Stanirowski PJ, Szukiewicz D, Pazura-Turowska M, Sawicki W, Cendrowski K. Placental expression of glucose transporter proteins in pregnancies complicated by gestational and pregestational diabetes mellitus. *Can J Diabetes*. 2018;42(2):209–217.
11. Al-Haggar M. Fanconi-Bickel syndrome as an example of marked allelic heterogeneity. *World J Nephrol*. 2012;1(3):63–68. https://doi.org/10.5527/wjn.v1.i3.63
12. Resnik R, Lockwood CJ, Moore TR, Greene MF, Copel JA, Silver RM. Creasy and Resnik's maternal-fetal medicine : principles and practice. In: *Maternal-fetal medicine*. Eighth edition. Philadelphia, PA: Elsevier; 2019.
13. Michau A, Guillemain G, Grosfeld A, et al. Mutations in SLC2A2 gene reveal hGLUT2 function in pancreatic β cell development. *J Biol Chem*. 2013;288(43):31080–31092. https://doi.org/10.1074/jbc.M113.469189
14. Hahn T, Hartmann M, Blaschitz A, et al. Localisation of the high affinity facilitative glucose transporter protein GLUT 1 in the placenta of human, marmoset monkey (Callithrix jacchus) and rat at different developmental stages. *Cell Tissue Res*. 1995;280(1):49–57. https://doi.org/10.1007/bf00304510
15. Wolf HJ, Desoye G. Immunohistochemical localization of glucose transporters and insulin receptors in human fetal membranes at term. *Histochemistry*. 1993;100(5):379–385. https://doi.org/10.1007/bf00268936
16. Barros LF, Yudilevich DL, Jarvis SM, Beaumont N, Baldwin SA. Quantitation and immunolocalization of glucose transporters in the human placenta. *Placenta*. 1995;16(7):623–633. https://doi.org/10.1016/0143-4004(95)90031-4
17. Sibiak R, Ozegowska K, Wender-Ozegowska E, Gutaj P, Mozdziak P, Kempisty B. Fetomaternal expression of glucose transporters (GLUTs)-Biochemical, cellular and clinical aspects. *Nutrients*. 2022;14(10):2025. https://doi.org/10.3390/nu14102025
18. Illsley NP. CURRENT TOPIC: glucose transporters in the human placenta. *Placenta*. 2000;21(1):14–22.
19. Jansson T, Cowley EA, Illsley NP. Cellular localization of glucose transporter messenger RNA in human placenta. *Reprod Fertil Dev*. 1995;7(6):1425–1430. https://doi.org/10.1071/rd9951425
20. Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. *Diabetes Metab Res Rev*. 2004;20(6):479–486. https://doi.org/10.1002/dmrr.482