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CASE REPORT

Multidisciplinary Management and Individualized Care in Pregnancy with Fanconi-Bickel Syndrome: A Case Report and Review of the Literature

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Abstract: Fanconi–Bickel syndrome (FBS) is a rare genetic disorder characterized by impaired glucose and galactose transport due to mutations in the SLC2A2 gene. It presents a broad phenotypic spectrum with initial nonspecific symptoms, often leading to missing or delayed diagnosis. The most common manifestations include failure to thrive, hepatomegaly, fasting hypoglycemia, postprandial hyperglycemia, significant glycosuria, proximal tubular nephropathy, osteoporosis and nutritional rickets. This study presents a rare case of pregnancy with FBS complicated with intrahepatic cholestasis and postprandial hyperglycemia, highlighting the challenges and complexities involved in managing such a high-risk pregnancy. A multidisciplinary team, including specialists in hepatology, nephrology, endocrinology, maternal-fetal medicine, and neonatology, collaborated to ensure optimal maternal and fetal outcomes. Through meticulous monitoring and individualized treatment strategies, pregnancy was successfully carried out at 37 weeks of gestation, culminating in favorable maternal and neonatal outcomes. All previously published cases of FBS were identified and compared to our case for a comprehensive analysis. This case highlights the critical role of specialized, multidisciplinary care in managing rare metabolic disorders during high-risk pregnancies and expands our current understanding of FBS treatment approaches and the management of specific manifestations. This underscores the need for a systematic approach to patient evaluation and management, ensuring timely identification of complications and tailored interventions to optimize maternal and fetal outcomes.

Keywords: Fanconi–Bickel syndrome, SLC2A2 gene mutations, glycogen storage disease, pregnancy

Introduction

Fanconi–Bickel syndrome (FBS), also known as glycogen storage disease type XI (GSD XI), is an autosomal recessive inherited disorder, that was initially described in 1949.[1] It is caused by many different mutations in the gene *SLC2A2*, which encodes glucose transporter membrane protein-2 (GLUT2) and is predominantly expressed in different tissues such as hepatocytes, pancreatic beta cells, intestinal epithelial cells and renal proximal tubular cells.[2] It is characterized by its low-affinity but high-capacity glucose transport properties, which enable rapid bidirectional movement of glucose and galactose across cell membranes in response to concentration gradients.[3]

GLUT2 plays a central role in glucose and galactose homeostasis across multiple organs. In the liver, it enables bidirectional glucose flux, supporting glycogen storage postprandially and glucose release during fasting. Loss of this function leads to hepatic glycogen accumulation, hepatomegaly, and dysregulated blood glucose levels.[4,5] In pancreatic β-cells, GLUT2 acts as a key glucose sensor for insulin secretion, and its dysfunction impairs normal insulin regulation.[6] In the renal proximal tubules, GLUT2 mediates glucose reabsorption. Defective transport results in glucosuria and generalized proximal tubular dysfunction consistent with FBS.[7] In the intestine, GLUT2 facilitates dietary glucose and

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galactose absorption into the portal circulation. Impaired function may contribute to carbohydrate malabsorption and metabolic dysregulations.[8]

FBS is a rare metabolic condition characterized by a broad phenotypic spectrum with significant variability in presentation, development of symptoms and severity, and overlaps with more common conditions, making the clinical diagnosis challenging.[9] The main common clinical features at presentation include general failure to thrive, hepatomegaly secondary to hepatorenal glycogen accumulation and impairment of glucose and galactose tolerance, fasting hypoglycemia and postprandial hyperglycemia, significant glycosuria, proximal tubular nephropathy and later life findings such as osteoporosis and nutritional rickets.[9–11]

This study describes the rare case of a 29-year-old pregnant woman affected by a mild form of FBS and details the laboratory and complex therapeutic management throughout her high-risk pregnancy. The identification of a pathogenic SLC2A2 mutation in the patient confirms the molecular basis of FBS and provides a unifying explanation for the constellation of clinical findings, including renal tubular dysfunction leading to proximal renal tubular acidosis and glycosuria, and impaired glucose handling. Understanding the specific impact of the SLC2A2 mutation elucidates the pathophysiological mechanism underlying the patient's metabolic derangements and supports the rationale for targeted dietary and supportive management.

Case Presentation

Our patient, a member of a highly consanguineous Druze family in central Galilee (Israel), was referred at age 5 for further evaluation of renal glycosuria, hypercalciuria and generalized aminoaciduria and was diagnosed with autosomal recessive proximal tubulopathy and hypercalciuria (ARPTH), a syndrome previously not described in the literature.[12] Subsequent genome-wide homozygosity mapping revealed a novel homozygous missense mutation c.372A>C in GLUT2, resulting in the substitution of an evolutionarily conserved arginine in the first intracellular loop with a serine (R124S).[13] This mutation occurs in the gene associated with FBS, which can manifest with a wide array of clinical and biochemical presentations, potentially due to the compromised expression of renal sodium-phosphate cotransporter 2c (Npt2c) within the proximal tubules.[13]

At age 24, she presented to our hepatology clinic due to prolonged elevation of liver enzymes. She was unaware of her genetic condition, largely because of the transition from handwritten archived medical records to electronic records over time, as well as strict medical confidentiality policies regarding the reporting of genetic diseases. A preliminary investigation was conducted, encompassing comprehensive laboratory blood tests, abdominal ultrasound, abdominal CT-scans and magnetic resonance imaging (MRI), revealing concurrent renal and hepatic abnormalities, including manifestations of proximal tubulopathy, generalized aminoaciduria, hypouricemia, uricosuria, hypercalciuria, nephrocalcinosis, and elevated liver enzymes without associated organomegaly. The patient did not present any growth retardation and demonstrated normal cognitive and intellectual development. Her body mass index (BMI) fell within the normal low range. Bone density assessments revealed osteopenia without osteoporosis. She reported a history of consuming a high-sugar diet during adulthood. Consequently, dietary interventions were advised to reduce sugar intake, which notably impacted liver function as evidenced by decreased transaminase levels. Extensive primary liver investigations, including liver biopsy, revealed no abnormalities despite the anticipated presence of signs indicating increased glycogen storage. The diagnosis was achieved through whole exome genetic sequencing, identifying a mutation in the SLC2A2 gene encoding GLUT2 (homozygous mutation c.372A>C), which is consistent with FBS.

At age 28, she sought consultation regarding pregnancy and preconception risk assessment. A review of the literature revealed four documented cases of pregnancy in individuals with Fanconi Bickel Syndrome (FBS), all of which culminated in successful deliveries. Her husband does not carry the same recessive genetic variant. While the possibility of having a child affected by this condition is very low, there is a 25% risk of inheriting her genetic variant and becoming a carrier. Given these reports, she was advised to proceed with pregnancy under a multidisciplinary team including obstetricians, nephrologists, dieticians, and hepatologists, to ensure optimal management of her condition and promote the best possible outcome for both the mother and the child.

Spontaneous pregnancy occurred after one year of attempting to conceive, coinciding with the initiation of investigations for potential fertility issues. Blood and urine test results just before conceiving were compatible with her disease

related findings including glycosuria, proteinuria, normal kidney function tests, normal electrolytes in blood (Na, K, Ca, Ph, Cl, Mg), very low uric acid levels in blood (1.5 mg/dl) with high fractional excretion of uric acid, a normal CBC, normal hemoglobin A1c (HgA1c) (5.3%), normal thyroid function tests, mild hyperlipidemia according to the lipid profile (cholesterol=218, triglycerides=80, HDL=59, LDL=140, nonHDL=159 mg/dl), and mildly elevated transaminases (AST=42, ALT=82 IU/l).

The first trimester of pregnancy was uneventful with routine monitoring. The baseline laboratory findings were consistent with her known disease manifestations, including glycosuria, mild proteinuria, low uric acid levels, and mildly elevated transaminases. Given her chronic kidney disease and proteinuria exceeding 300 mg/24 h, she was classified as high risk, prompting the initiation of aspirin therapy.

In the second trimester, the patient presented with metabolic complications of proximal tubulopathy, including normal anion gap metabolic acidosis secondary to bicarbonaturia. To address this, sodium bicarbonate supplementation was initiated and titrated in escalating doses to maintain normal bicarbonate levels appropriate for pregnancy. Additionally, she was started on vitamin D supplementation, as proximal tubulopathy is thought to reduce 1α-hydroxylase activity, impairing the activation of vitamin D. To compensate for this deficiency, she was prescribed alfacalcidol (α-D3). Multivitamin supplementation was also introduced to support overall maternal and fetal health. A dietician guided carbohydrate intake to optimize glucose metabolism. Proteinuria increased during pregnancy due to pregnancy-related hemodynamic changes, including increased plasma volume and intraglomerular pressure, which may further exacerbate proteinuria. Close monitoring is essential, as a significant increase in proteinuria may signal the need for therapeutic interventions to mitigate potential complications such as worsening renal function, hypertension, or adverse pregnancy outcomes.

At 30 weeks, the patient developed impaired fasting glucose (IFG) and postprandial hyperglycemia, prompting the initiation of low-dose basal insulin Detemir (Levemir), in conjunction with her disease-specific dietary regimen. To avoid exposing the patient to a high sugar load (100 g), we opted against the oral glucose tolerance test, instead relying on continuous blood glucose monitoring by an electronic glucometer to guide insulin dose adjustments on the basis of glucose fluctuations. However, under this regimen, the patient experienced an episode of subclinical hypoglycemia, with glucose levels recorded at 69 mg/dL, necessitating Detemir dosage adjustments.

At 34 weeks, she developed intrahepatic cholestasis of pregnancy (ICP), with elevated bile salts (>50 mol/L) and triglycerides (>700 mg/dL). High levels postprandial bile salts were also measured (117 mol/L) in one instance. Consequently, therapeutic intervention involving ursodeoxycholic acid was initiated, yielding symptomatic relief and subsequently, the concentration of bile salts decreased to 23,7 mol/L. Given the very high triglyceride levels, fibrate therapy was initiated to further alleviate ICP symptoms and reduce the risk of pancreatitis. Owing to the severity of ICP, which is associated with a 3% risk of late intrauterine demise (IUD), the fetus was placed under intensive monitoring. However, elevated lipid levels were detected in the third trimester and persisted, yielding cholesterol levels exceeding 340 mg/dl and triglycerides above 1900 mg/dl, without clinically observed complications. The serum calcium, phosphate, and magnesium levels remained stable, with hypercalciuria detected only in the first trimester.

Her kidney function test was still normal during pregnancy with decreasing creatinine levels, as expected, with hyperfiltration during pregnancy, and proteinuria slightly increased toward the third trimester. Urine cultures were performed without any evidence of urinary tract infections. The level of alfa fetoprotein was measured once during the second trimester and was within the normal limits (5.8) similar to the levels before conception. Pancreatic enzymes, including lipase and amylase were also measured within the normal range, with the lowest levels observed in the late third trimester.

Urine analysis revealed hypercalciuria in the first trimester only. Serum calcium and phosphor levels were normal during the three trimesters. While very low blood uric acid levels were observed in the first trimester, the levels reached low normal ranges during the third trimester. Blood magnesium levels were within the normal range before conception and during the three trimesters. At 36 weeks, the obstetric team recommended delivery, but the patient declined. However, at 37 weeks and 1 day, labor was induced, leading to the vaginal delivery of a healthy female newborn (2785 g) without complications. The newborn exhibited no hypoglycemia or respiratory distress syndrome. Postpartum

monitoring revealed a return of proteinuria and lipid levels to baseline. Detailed blood test results before, during pregnancy and shortly after delivery are provided in Table 1.

This case represents a comprehensive analysis of laboratory and clinical data pertaining to a pregnancy experienced by a 29-year-old female afflicted with a mild form of FBS. It is distinctive in several aspects. This is the first instance within the literature to document notable elevations in lipid profile parameters in association with FBS syndrome during pregnancy beyond the described levels in normal pregnancies with a return to baseline after delivery. Lipid levels during pregnancy and the magnitude of these changes during pregnancy are influenced by many factors, including prepregnancy lipid levels, BMI, age, diet, and ethnicity.[14–16] In early normal pregnancy, the lipid profile can be disrupted, with slightly

Table 1 Laboratory Findings Before Conception, During Pregnancy and After Delivery

Laboratory Tests	Before Conception	First Trimester	Second Trimester	Third Trimester	After Delivery (2 Months)
Kidney function tests					
Creatinine (mg/dl)	0.65	0.45	0.48	0.88	0.63
GFR (mL/min)				88	
Urea (mg/dl)	42	34	38	23.99	
Uric Acid (mg/dl)	1.51	2.19	2.25	3.5	1.77
Liver function tests					
AST (IU/L)	42	25	18	38	57
ALT (IU/L)	82	44	20	27	143
ALKP (IU/L)	156	110	91	343	362
Bilirubin Total (mg/dl)	0.51	0.26	0.23	0.3	0.44
GGT (IU/L)	200	84	35	90	285
Albumin (g/dl)	4.7	4.4	4.12	2.89	4.6
Total protein (g/dl)	7.7	7.2	6.9	6.68	7.5
LDH (IU/L)	231	130		192	133
CPK (IU/L)	34	28	21	29	44
Bile salts (micromol/L)	N/A	N/A	N/A	117(max)	
Lipid profile					
Cholesterol (mg/dl)	215	231	259	399	222
Triglycerides (mg/dl)	80	121	198	1931	95
HDL Cholesterol (mg/dl)	59	92	86	31	62
Non HDL Cholesterol (mg/dl)	156	139	173	372	161
Hematologic profile					
WBC (K/mL)	5.1	8.1	8.3	6.9	5.8
Hemoglobin (g/dl)	13.5	12.4	11.3	13.0	12.5
Platelets (K/mL)	247	222	238	218	269
INR (IU)	1.04			0.8	
Electrolytes					
Sodium (mEq/L)	137	136	135	134	138
Potassium (mEq/L)	4.3	4.3	4.0	3.75	4.0
Phosphor (mg/dl)	2.98	3.06	3.18	2.57	4.09
Calcium (mg/dl)	9.18	10.49	10.08	9.35	9.59
Chloride (mg/dl)	105	105	105	106	
Magnesium (mg/dl)	2.19		1.9	2.18	2.11
Glucose profile					
FG (mg/dl)	88	111	83	110	85
HgA1c (%)	5.3		5		4.9

(*Continued*)

Table 1 (Continued).

Laboratory Tests	Before Conception	First Trimester	Second Trimester	Third Trimester	After Delivery (2 Months)
Hormones and Vitamin profile					
TSH (mIU/L)	2.5		3.03	2.34	2.65
17-hydroxyprogesteron (nmol/l)	1.6			33	
DHEA sulphate (mcmol/L)	4.3				
Estradiol (pg/mL)	206			125,684	
Progesterone (ng/mL)	1.8			1076	
Vitamin D level	36		36	50	76
Iron profile					
Iron (mcg/dl)	138	136	146		
Ferritin (ng/mL)	70	76	144		132
Transferrin (mg/dl)	269		291		267
Urine analysis					
Glucose strip (mg/dl)	>1000	>1000	>1000	>1000	
Ketones strip	Neg	Neg	Neg	Neg	
Protein strip (mg/dl)	20				
Protein (mg/24 h)	450	568	708	768	
Creatinine (mg/24 h)		698	634	723	
Calcium (mg/24 h)		505	292	266	
Magnesium (mg/24 h)	108	202			
Phosphor (mg/24 h)	779	946			
Urine culture	Neg	Neg	Neg	Neg	
Venous blood gases					
PH	N/A	7.38	7.366	7.32	
HCO3, Bicarbonates (mEq/L)	N/A	20.7	20.2	19	
Actual base excess	N/A	−3.6	−4.4	−6.3	

Abbreviations: GFR, glomerular filtration rate, AST, aspartate aminotransferase, ALT, alanine aminotransferase, ALKP, alkaline phosphatase, GGT, gamma-glutamyltransferase, LDH, lactate dehydrogenase, CPK, creatine phosphokinase, HDL, high-density lipoprotein, WBC, white blood cell; INR, international normalized ratio, PPG, postprandial glucose, FG, fasting glucose, TSH, thyroid stimulating hormone, DHEA, dehydro-epiandrosterone.

decreased levels in the first trimester and increased levels from the second trimester until the end of term. Total cholesterol and LDL-C levels increased by approximately 30–50% while triglycerides increased by approximately 50–100% and HDL-C levels and apolipoprotein A1 (apoA1) increased by 20–40% from early pregnancy onward with a plateau at approximately 20–24 weeks.[17,18]

Despite presenting with predominant hepatic and renal clinical manifestations and laboratory findings indicative of dysglycemia and glucose storage anomalies, it delineates the occurrence of gestational diabetes mellitus (GDM), with prompts the initiation of insulin therapy, albeit amid debate due to the patient's presentation of a normal HbA1c percentage and the high risk of hypoglycemia in such cases. Notably, this is the second reported case complicated by ICP, necessitating therapeutic interventions. Electrolytes in urine were not detected in any of the previous cases during pregnancy. Water and electrolytes replacement on the basis of urinary losses, vitamin D and multivitamin supplementation and nutritional management with slowly absorbed carbohydrates contributed to a fairly good prognosis of the disease.

Literature Review

Information regarding childbearing status and pregnancy outcomes in individuals with FBS is limited. A published literature search using the terms "FBS" "pregnancy" and "reproduction" in the PubMed database yielded only four reports documenting reproduction among individuals with FBS. Another additional case recently reported was noted during the preparation of this manuscript. The details previously reported pregnancy cases are provided in Table 2.

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Table 2 Reported Cases of Pregnancy in FBS Syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5
Reference	Pena et al,[13]	Ke˛dzierska et al,[14]	Carli et al,[15]	DeLeon et al,[16]	Szmuilowicz et al,[17]
Age (year)	31	31	38	22	27
BMI (kg/m^2)	28			46.47	31.8
Consanguinity	No (Caucasian)		No (Caucasian)		
Genotype	Missense mutation (c. 1439 C>G, p.T480R) in one allele. Frameshift mutation leading to premature stop codon (c.1469delA,p.L490SfsX24) in the 2nd allele	Deletion (1-bp) in exon 1 and mutation in an acceptor "splice-site" of intron 8	Homozygous mutation 889 C-T encoding GLUT-2		
Phenotype	- Glucosuria, proteinuria, impaired tubular reabsorption of phosphate and hypercholes-terolemia - Osteopenia (DXA) - Hepatomegaly resolved at age 18 - Menarche at age 15	- Short stature (height=135 cm) - Motor development normal - Normal liver function - Acute renal failure at age 4 - Bilateral kidney stones - Osteodystrophy - Tendency to fasting hypoglycemia and postprandial hy-perglycemia	- Short stature (height=148 cm) - Weight impaired - Increased kidney echogenici-ty - Normal kidney function - No metabolic disorders - Osteoporosis at age 28 - Mild hepatomegaly with initial steatosis by US - glycosuria, proteinuria	- Short stature - Rickets - Congenital aortic root dilation. - Normal lumbar spine exam but degenerative changes on X-ray	- Short stature (height=117 cm) - Rickets - Osteomalacia - Proximal renal tubular acidosis complicated by hypophos-phatemia and hypokalemia
Major lab findings	- Glucosuria, galactosuria, pro-teinuria - Generalized aminoaciduria - Impaired phosphate tubular reabsorption - Impaired glucose tolerance - HgA1c level marginally elevated - Serum phosphate and calcium levels normal - Alkaline phosphatase levelsnormal	- High blood BUN= 63.0 mg/dL - High creatinine = 2.7 mg/dL - Low GFR = 21 mL/min/1.73m^2 - Fasting hypoglycemia and postprandial hyperglycemia - HbA1c normal	- Glycosuria, proteinuria, mild Hypokalemia - HbA1c at term = 30 mmol/mol	- low calcium at 8.2 mg/dL - Elevated Alkp (259 IU/L) - Low total protein 6.0 g/dL - Normal liver enzymes - Normal coagulation	- Fasting hypoglycemia and postprandial hyperglycemia - HbA1c 5.9%
Treatment	Multivitamins and supplements	- Potassium - Bicarbonates - Active Vitamin D - Aspirin - Ursodeoxycholic acid - Promethazine - Phenobarbital - Iron supplements - Hemodialysis stopped after delivery	- Oral potassium - Vitamin D - Calcium supplement - Biphosphonate	- Calcitriol - Calcium - Potassium-phosphate - Potassium-chloride - supplemental tube feeds through a G-tube	- Cornstarch therapy and MNT based on CGM
Pregnancy outcome	- Healthy boy newborn - GDM treated with diet - Cesarean section - Impaired glucose tolerance after her pregnancy - No detailed laboratory records reported during pregnancy	- Healthy boy newborn - Cholestasis of pregnancy - Postprandial hyperglycemia treated with diet - Hemodialysis therapy - Polyhydramnios at 23 weeks. - Cesarean section 34 week	- Healthy girl newborn (3.18 kg) - Urine excretion and proteinuria progressively returned to usual range after delivery	- Healthy newborn - 37 Week gestation - GDM treated with insulin - Hypoglycemic episodes - Neuraxial anesthesia - Cesarean delivery proceeded uneventfully	- Healthy female newborn (3.45 kg) treated for hypogly-cemia - 38 Week gestation - Cesarean delivery proceeded uneventfully

Abbreviations: GDM, gestational diabetes Mellitus, DXA, dual-energy X-ray absorptiometry, HgA1c, Hemoglobin A1c, Glut2, Glucose transporter 2, G-tube, gastric tube, CGM, continuous glucose monitoring, MNT, medical nutrition therapy.

1. Pena et al. A 31-year-old woman with diet-controlled GDM delivered a healthy boy via C-section. There are no records of laboratory tests conducted during pregnancy.[19]
2. Ke˛dzierska et al reported a 31-year-old patient with FBS, which was complicated by renal failure requiring dialysis and postprandial hyperglycemia treated with a diet alone. Delivery by C-section was due to the presence of polyhydramnios.[20]
3. Carli et al reported a 38-year-old patient with FBS who experienced an uncomplicated pregnancy. She delivered a healthy girl newborn at 40 weeks and 3 days of gestation via normal delivery.[21]
4. DeLeon et al described a 22-year-old patient who was diagnosed with FBS, and who exhibited rickets as a manifestation of her condition. This report aimed to elucidate the rationale behind the anesthetic choices employed during cesarean section, which significantly contributed to achieving a successful outcome.[22]
5. The latest report describes a 27-year-old patient with a previous history of pregnancy with a miscarriage at age 22 and a term cesarean section at age 23 (not published). This focused on continuous glucose monitoring-derived glycemic patterns and specific guidance for cornstarch therapy and medical nutrition therapy for the treatment of FBS-associated dysglycemia, allowing the avoidance of insulin therapy.[23]

Discussion

While the symptoms associated with FBS do not appear to hinder reproduction in affected individuals,[21] these case reports document instances of successful pregnancies in six affected women. They underscore a range of clinical considerations relevant to individuals affected by the syndrome, emphasizing the crucial need to consider data and procedures to ensure optimal fetal and maternal outcomes in this complex disease.

The manifestations of FBS during pregnancy can vary and may not always result in complications. Therefore, a collaborative approach involving obstetric care and the expertise of various specialists before, during, and after pregnancy is strongly recommended, ensuring vigilant surveillance for complications such as GDM, cholestasis, deteriorating renal function, nephrolithiasis, urinary tract infections related to constant glycosuria and increasing the risk of premature birth, and obstetrical complication delivery outcomes.

GDM, a characteristic feature inherent to the disease that may be exacerbated during pregnancy due to hormonal alterations associated with the physiological state, is the most prevalent complication among the patients under consideration. Postprandial hyperglycemia serves as the primary indicator of GDM, notwithstanding the presence of normal levels of HbA1c.

To date, there is a lack of empirical evidence suggesting that elevated postprandial glycemia in mothers influences fetal development. Given the presence of normal HgA1c levels alongside a minor elevation in fasting glucose, we advocate managing this phenomenon through dietary interventions emphasizing the consumption of slowly absorbed carbohydrates. Additionally, the judicious use of insulin therapy, mainly short-acting types (postprandial effects), is recommended, particularly in cases where glycemic control is challenging, to mitigate the risk of induced hypoglycemia.

Two of the mentioned pregnant patients with FBS were complicated by ICP, successfully treated with drugs and delivered after 37 weeks of gestation. The ICP incidence rate is between 0.2 and 2% of all pregnancies,[24] varies with ethnicity and geographic distribution, and is higher among patients with chronic liver disease.[25,26] ICP arises from disruptions in biliary lipid secretion, potentially influenced by the actions of endogenous steroids. Several authors have suggested that ICP is probably associated with the overproduction of some sulfated progesterone metabolites.[27,28] It is not possible to explain this phenomenon just by considering the presented data; however, the high 17-hydroxyprogesterone levels measured in our case may indicate the anticipated effect of pregnancy hormones in FBS. These findings highlight the need to closely monitor symptoms and signs of worsening hepatic disease in FBS patients during late pregnancy. To date, this is the first report documenting notable elevations in lipid profile parameters beyond the described levels in normal pregnancies with a return to baseline after delivery.

As a result of the physiological state, renal plasma flow and the glomerular filtration rate increase during pregnancy. Increased urinary excretion of calcium, uric acid, sodium, and oxalate, all of which are lithogenic.[29,30] Most patients with FBS suffer from polydipsia and polyuria and develop chronic kidney disease later in life, nephrocalcinosis or bilateral nephrolithiasis, resulting mainly from hypercalciuria, which is the leading cause.[31] Hyperphosphaturia, as an

accompanying entity, can exacerbate this problem. One of the patients presented with urolithiasis or kidney stone symptoms, during pregnancy. Complicated nephrolithiasis can occur before conception, and renal function deteriorates during pregnancy, resulting in the need for dialysis treatment.

Conclusion

This report highlights the complexity of managing rare inherited metabolic disorder affecting multiple organ systems and extends the current knowledge about FBS treatment approaches during pregnancy. Close laboratory monitoring, water and electrolyte replacement on the basis of urinary loss, vitamin D and multivitamin supplementation, nutritional management with slowly absorbed carbohydrates and judicious and close control of insulin administration contributed to a fairly good prognosis of the disease. Given its multisystem involvement, effective management requires a structured, multidisciplinary approach involving endocrinologists, hepatologists, nephrologists, geneticists, and dietitians. Awareness of inherited metabolic disorders like FBS and its early recognition are especially important for appropriate genetic counseling, risk stratification, and monitoring of metabolic status in both the mother and fetus.[32] This report underscores the importance of a comprehensive prenatal evaluation and careful postpartum monitoring, enabling timely initiation of dietary modifications and supportive treatment to optimize growth and metabolic balance.

Abbreviations

FBS, Fanconi–Bickel syndrome; GLUT2, glucose transporter membrane protein-2; ARPTH, autosomal recessive proximal tubulopathy and hypercalciuria; MRI, magnetic resonance imaging; BMI, body mass index; IFG, impaired fasting glucose; IC, intrahepatic cholestasis of pregnancy; IUD, intrauterine demise; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALKP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; WBC, white blood cell; INR, international normalized ratio; PPG, postprandial glucose; FG, fasting glucose; TSH, thyroid stimulating hormone; DHEA, dehydroepiandrosterone; apoA1, apolipoprotein A1; GDM, gestational diabetes mellitus; DXA, dual-energy X-ray absorptiometry; HgA1c, hemoglobin A1c; G-tube, gastric tube; CGM, continuous glucose monitoring; MNT, medical nutrition therapy.

Ethical Approval

Only one case was presented not requiring approval from our Ethics Committee (Galilee Medical Centre, Nahariyah). Clinical trial number is not applicable.

Consent

Informed written consent has been obtained from the patient for publication of her clinical details.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Fanconi G, Bickel H. Chronic aminoaciduria (amino acid diabetes or nephrotic-glucosuric dwarfism) in glycogen storage and cystine disease. *Helv Paediatrica Acta*. 1949;4:359–396.
2. Santer R, Schneppenheim R, Dombrowski A, Götze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with fanconi-bickel syndrome. *Nat Genet*. 1997;17:324–326.
3. 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;21:6286.
4. Mueckler M, Thorens B. The SLC2 (GLUT) family of membrane transporters. *Mol Aspects Med*. 2013;34:121–138. doi:10.1016/j.mam.2012.07.001
5. Sato H, Miyamoto S, Sasaki N. Liver abnormality in Turner syndrome. *Eur J Pediatr*. 2001;160:59. doi:10.1007/s004310000634
6. Thorens B. GLUT2, glucose sensing and glucose homeostasis. *Diabetologia*. 2015;58:221–232.
7. Santer R, Steinmann B, Schaub J. Fanconi-bickel syndrome-a congenital defect of facilitative glucose transport. *Current Mol Med*. 2002;2:213–227. doi:10.2174/1566524024605743
8. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. *Pflügers Archiv*. 2004;447:510–518. doi:10.1007/s00424-003-1202-0

9. Gupta N, Nambam B, Weinstein DA, Shoemaker LR. Late diagnosis of fanconi-bickel syndrome: challenges with the diagnosis and literature review. *J Inborn Error Metabol Screen*. 2016;4:2326409816679430. doi:10.1177/2326409816679430
10. Manz F, Bickel H, Brodehl J, et al. Fanconi-Bickel syndrome. *Pediatr Nephrol*. 1987;1:509–518. doi:10.1007/BF00849262
11. Santer R, Groth S, Kinner M, et al. The mutation spectrum of the facilitative glucose transporter gene SLC2A2 (GLUT2) in patients with Fanconi-Bickel syndrome. *Hum Genet*. 2002;110:21–29. doi:10.1007/s00439-001-0638-6
12. Magen D, Adler L, Mandel H, Efrati E, Zelikovic I. Autosomal recessive renal proximal tubulopathy and hypercalciuria: a new syndrome. *Am J Kidney Dis*. 2004;43:600–606. doi:10.1053/j.ajkd.2003.12.024
13. Mannstadt M, Magen D, Segawa H, et al. Fanconi-Bickel syndrome and autosomal recessive proximal tubulopathy with hypercalciuria (ARPTH) are allelic variants caused by GLUT2 mutations. *J Clin Endocrinol Metab*. 2012;97:E1978–E1986. doi:10.1210/jc.2012-1279
14. Baas RE, Hutten BA, Henrichs J, Vrijkotte TG. Associations between maternal lipid blood levels at the 13th week of pregnancy and offspring's adiposity at age 11-12 years. *J Clin Endocrinol Metab*. 2022;107:e4048–e4057.
15. Bever AM, Mumford SL, Schisterman EF, et al. Maternal preconception lipid profile and gestational lipid changes in relation to birthweight outcomes. *Sci Rep*. 2020;10:1374. doi:10.1038/s41598-019-57373-z
16. Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Clin Exp Obstet Gynecol*. 2005;193:1292–1301. doi:10.1016/j.ajog.2005.05.016
17. Roeters van Lennep JE, Tokgözoğlu LS, Badimon L, et al. Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society. *Eur Heart J*. 2023;44:4157–4173.
18. Wu L, Wu Q, Li Q, et al. Consecutive reference intervals for biochemical indices related to serum lipid levels and renal function during normal pregnancy. *BMC Pregnancy Childbirth*. 2022;22:642.
19. Pena L, Charrow J. Fanconi–Bickel syndrome: report of life history and successful pregnancy in an affected patient. *Am J Med Genet A*. 2011;155:415–417.
20. Kędzierska K, Kwiatkowski S, Torbé A, et al. Successful pregnancy in the patient with Fanconi-Bickel syndrome undergoing daily hemodialysis. *Am J Med Genetics-Part A*. 2011;155:2028–2030. doi:10.1002/ajmg.a.34099
21. Carli M, Probizer PR, Tateo S. Successful pregnancy and vaginal birth in a patient with Fanconi-Bickel Syndrome–case report and literature review. *Clin Exp Obstet Gynecol*. 2018;45:138–140. doi:10.12891/ceog4100.2018
22. DeLeon AM, Gaiha RD, Peralta FM. The successful anesthetic management of a cesarean delivery in a patient with fanconi–bickel syndrome. *Case Reports Anesthesiol*. 2022;2022:3220486. doi:10.1155/2022/3220486
23. Szmuilowicz ED, Fruzyna E, Madden N, et al. Management of dysglycemia in a pregnancy complicated by fanconi–bickel syndrome. *AACE Clin Case Rep*. 2024;10:224–228. doi:10.1016/j.aace.2024.07.008
24. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. *Obstetrics Gynecol*. 2014;124:120–133.
25. Floreani A, Gervasi MT. New insights on intrahepatic cholestasis of pregnancy. *Clin Liver Dis*. 2016;20:177–189. doi:10.1016/j.cld.2015.08.010
26. Marschall HU, Wikström Shemer E, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. *Hepatology*. 2013;58:1385–1391. doi:10.1002/hep.26444
27. Reyes H. Sex hormones and bile acids in intrahepatic cholestasis of pregnancy. 2008;47:376–379.
28. Reyes H, Sjövall J. Bile acids and progesterone metabolites intrahepatic cholestasis of pregnancy. *Annals med*. 2000;32:94–106. doi:10.3109/07853890009011758
29. Maikranz P, Holley JL, Parks JH, Lindheimer MD, Nakagawa Y, Coe FL. Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations. *Kidney Int*. 1989;36:108–113. doi:10.1038/ki.1989.168
30. Smith C, Kristensen C, Davis M, Abraham P. An evaluation of the physicochemical risk for renal stone disease during pregnancy. *Clin nephrol*. 2001;55:205–211.
31. Haffner D, Weinfurth A, Manz F, et al. Long-term outcome of paediatric patients with hereditary tubular disorders. *Nephron*. 1999;83:250–260. doi:10.1159/000045518
32. Blau N, Duran M, Gibson KM, Vici CD. Physician's guide to the diagnosis, treatment, and follow-up of inherited metabolic diseases. *Springer*. 2014;213.